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ABOGADOS

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Señor Jefe

DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Santa Fe de Bogotá, D.C.

SUPERINDUSTRIA Y COMERCIO
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02-01-09

Re.: Expediente No. 00 – 26.419

Solicitud de Patente

BEECHAM PHARMACEUTICALS PTE LIMITED

Debidamente traducidas, adjunto acompaño las copias oficiales de las solicitudes de patente estadounidenses

No. 60/129.074

No .60/150.727

No. 60/159.813

las cuales le solicito agregar a este expediente para los efectos legales respectivos.

De Usted atentamente,

GERMAN CASTILLO GRAU

T.P.#2.978 del C.S.J.

AN92

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ESTADOS UNIDOS DE AMERICA

A TODOS AQUELLOS A QUIENES LLEGUEN LOS PRESENTES:

MINISTERIO DE COMERCIO DE ESTADOS UNIDOS

Oficina de Patentes y Marcas Registradas de Estados Unidos

6 de abril de 2000

SE CERTIFICA QUE SE ADJUNTA AL PRESENTE DOCUMENTO UNA COPIA FIEL DE LOS ARCHIVOS DE LA OFICINA DE PATENTES Y MARCAS REGISTRADAS DE ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA QUE CUMPLIÓ LOS REQUISITOS PARA OTORGARLE UNA FECHA DE REGISTRO BAJO EL TITULO 35 DEL CODIGO DE ESTADOS UNIDOS NUMERAL 111.

NUMERO DE SOLICITUD: *60/129.074*

FECHA DE REGISTRO: *13 de abril de 1999*

(Sello de oblea)

Por Autoridad del

COMISIONADO DE PATENTES Y MARCAS REGISTRADAS

(Firma ilegible)

H. L. JACKSON

Funcionario que Certifica

Mmu/mvr

"CERTIFICADO DE CORREO EXPRESO"
Número Etiqueta Porte "Correo Expreso" **EL175489846US**
Fecha de Depósito: **ABRIL 13, 1999**
Por el presente certifico que este Documento o Derecho se está depositando en el mencionado Servicio Postal de los Estados Unidos " Correo Expreso Ofician Postal a Destinatario" servicio bajo 37 CFR 1.10 en la fecha arriba indicada y va dirigido a: Comisionado Asistente para Patentes, Washington, D.C. 20231.
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HOJA DE REMISION DE SOLICITUD PROVISIONAL

Esta es una solicitud para registrar una SOLICITUD PROVISIONAL de PATENTE bajo 37 CFR 1.53©.

Causa No.	P32276P		

INVENTOR(es) / SOLICITANTE(s) Apellido	Primer Nombre	Inicial Media	Residencia (Ciudad y estado o país extranjero)
Storm	Kevin	H.	Bristol, Tennessee, USA

TITULO DE LA INVENCION (280 caracteres máx.)
FORMULACION FARMACEUTICA

DIRECCION DE CORRESPONDENCIA
SMITHKLINE BEECHAM CORPORATION
Corporate Intellectual Property – UW2220
709 Swedeland Road
King of Prussia
Teléfono No. 610-270-5017
Fax No. 610-270-5090

Estado	PA	Código Postal	19406-2799	País	Estados Unidos de América

PARTES DE SOLICITUD ADJUNTAS (marque todo lo que aplica)

☒ Especificación	Número de páginas	19	☐ Declaración Pequeña Entidad
☒ Dibujos	Número de hojas	1	☐ Otro (especifique)

METODO PAGO PARA REGISTRO DERECHOS ESTA SOLICITUD PROVISIONAL DE PATENTE
☒ Por el presente documento el Comisionado está autorizado a cobrar derechos de registro y abonarlos a la Cuenta de Depósito No. **19-2570** DERECHO POR REGISTRO PROVISIONAL ($) **$150,00**

La invención se realizó por medio de una agencia del Gobierno de los Estados Unidos o bajo contrato con una agencia del Gobierno de los Estados Unidos.
☒ No.
☐ Sí, el nombre de la agencia del gobierno de los Estados Unidos y el número del contrato son: _____

Presentado respetuosamente,
Firma: *Firma ilegible* Fecha: 13 ab 99
Dara L. Dinner Registro No.: **33680**

☐ Inventores adicionales nombrados en hojas numeradas por separado que aquí se adjuntan.

UNICAMENTE SOLICITUD PROVISIONAL DE REGISTRO

ENVIESE A: Comisionado Asistente para Patentes, Buzón Solicitud Provisional, Washington, D.C. 20231

Reivindicaciones:

1. Una formulación de tableta que comprende amoxicilina y clavulanato de potasio donde todo el clavulanato de potasio y parte de la amoxicilina se encuentra en una primera fase en la se libera inmediatamente y el resto de la amoxicilina en una segunda fase en la cual la amoxicilina es liberada lentamente.

2. Una formulación de tableta que comprende clavulanato de potasio y una primera parte de amoxicilina formulada con excipientes farmacéuticamente aceptables que permiten la inmediata liberación del clavulanato de potasio y la amoxicilina y comprende además una segunda parte de amoxicilina formulada con excipientes farmacéuticamente aceptables que permiten la lenta liberación de la amoxicilina.

3. Una formulación de tableta según la reivindicación 1 donde el perfil farmacocinético de las tabletas proporcionará un valor de amoxicilina C_{max} de al menos 12 µg/ml en el plasma humano.

4. Una tableta como la de la reivindicación 1 donde el perfil farmacocinético de las tabletas proporcionará una concentración de amoxicilina en plasma de al enos 4 µg/ml durante entre 5 y 7 horas.

5. Una formulación de tableta según la reivindicación 1 donde la amoxicilina y el clavulanato de potasio están presentes en una proporción por peso de 1:1 hasta 30:1.

6. Una formulación de tableta según la reivindicación 5 donde la amoxicilina y el clavulanato de potasio están presentes en una proporción por peso de10:1 a 20:1.

7. Una formulación de tableta según la reivindicación 5 donde la amoxicilina y el clavulanato de potasio están presentes en una proporción por peso de 13:1 a 16:1.

8. Una formulación de tableta según la reivindicación 5 donde la amoxicilina y el clavulanato de potasio están presentes en una proporción por peso de aproximadamente 14:1.

9. Una formulación de tableta según la reivindicación 1 donde la parte de

amoxicilina que es liberada inmediatamente se suministra como trihidrato de amoxicilina mientras que la parte de amoxicilina que es liberada lentamente se suministra como trihidrato de amoxicilina o amoxicilina de sodio o una mezcla de ambos.

10. Una formulación de tableta según la reivindicación 9 donde la amoxicilina se encuentra presente en las fases de liberación inmediata y lenta en una proporción de 3:1 a 1:3.

11. Una formulación de tableta según la reivindicación 10 donde la amoxicilina se encuentra presente en las fases de liberación inmediata y lenta en una proporción de 3:2 a 2:3.

12. Una formulación de tableta según la reivindicación 10 donde la amoxicilina se encuentra presente en las fases de liberación inmediata y lenta en una proporción de aproximadamente 1:1.

13. Una formulación de tableta según la reivindicación 1 que comprende amoxicilina y clavulanato de potasio en una proporción de 14:1, y comprende cerca de 438 mg de amoxicilina y cerca de 62.5 mg de clavulanato de potasio en la fase de liberación inmediata y cerca de 438 mg de amoxicilina en la fase de liberación lenta.

14. Una formulación de tableta según la reivindicación 1 donde las fases de liberación inmediata y lenta se suministran como capas separadas de una tableta por capas.

15. Una formulación de tableta según la reivindicación 14 donde la capa de liberación lenta comprende amoxicilina junto con un excipiente retardante de liberación que permite la lenta liberación de la amoxicilina.

16. Una formulación de tableta según la reivindicación 16 donde el excipiente retardante de liberación se selecciona de polímeros sensibles al pH; un polímero retardante de liberación con un alto grado de expansión cuando entra en contacto con el agua o medio acuoso; un material polimérico que forma un gel en contacto con el agua o medio acuoso; y un material polimérico que tiene ambas

características, que se expande y se gelifica cuando entra en contacto con agua o un medio acuoso.

17. Una formulación de tableta según la reivindicación 16 donde el polímero retardante de liberación que se gelifica se selecciona entre metilcelulosa, carboximetilcelulosa, hidroxipropilmetilcelulosa de bajo peso molecular, polivinilalcoholes de bajo peso molecular, polioxietilenoglicoles y polivinilpirrolidona con enlace no cruzado, goma arábiga.

18. Una formulación de tableta según la reivindicación 16 donde el polímero retardante de liberación que se gelifica es la goma arábiga.

19. Una formulación de tableta según la reivindicación 18 donde la goma arábiga constituye un grado de malla fina de la goma arábiga.

20. Una formulación de tableta según la reivindicación 19 donde la goma arábiga es goma arábiga de grado farmacéutico, de malla 200.

21. Una formulación de tableta según la reivindicación 18 donde la goma arábiga está presente de un 0.5 a un 10% por peso de la capa.

22. Una formulación de tableta según la reivindicación 14 donde la capa de liberación lenta comprende de un 70 a un 80% de amoxicilina, de un 0.5 a un 10% de goma arábiga, de un 10 a un 30% de materiales que ayudan a llenar y comprimir, y cantidades convencionales de lubricantes.

23. Una formulación de tableta según la reivindicación 22 donde la capa de liberación lenta comprende de un 70 a un 80% de amoxicilina, de un 1.0 a un 6% de goma arábiga, desde un 15 a un 30% de celulosa microcristalina, y de un 0.5 a un 1.5% de estearato de magnesio.

24. Un juego que comprende una tableta de liberación inmediata que contiene amoxicilina y clavulanato de potasio y una tableta de liberación lenta que contiene (sin clavulanato de potasio).

25. Una tableta farmacéutica que contien amoxicilina (como único ingrediente activo) formulada con un excipiente retardante de liberación que causa una liberación lenta de la amoxicilina de la tableta.

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26. Una tableta según la reivindicación 25 que comprende de 100 a 1250 mg de amoxicilina.

27. Una tableta según la reivindicación 25 donde el excipiente retardante de liberación es goma arábiga.

28. Una formulación de tableta según la reivindicación 25 donde la goma arábiga es goma arábiga de grado farmacéutico, malla 200.

29. Una formulación de tableta según la reivindicación 25 donde la goma arábiga se encuentra presente en un 0.5% a un 25% por peso de la capa.

30. Un método de tratamiento de las infecciones bacterianas en seres humanos que comprende la administración de una cantidad terapéuticamente efectiva de amoxicilina y clavulanato de potasio en una formulación de tableta que comprende una primera fase en la que todo el clavulanato de potasio y parte de la amoxicilina son liberados inmediatamente y una segunda fase que comprende el resto de la amoxicilina de la cual la amoxicilina se libera lentamente.

31. Un método según la reivindicación 30 donde la infección es causada por l os organismos *S pneumoniae* (incluido el *S pneumoniae* resistente a medicamentos), *H influenzae* y/o *M catarrhalis.*

32. Un método según la reivindicación 30 donde la formulación de tableta se toma en intervalos de dosificación de 12 horas.

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PA 229213

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

April 06, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/129,074***
FILING DATE: ***April 13, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

H. L. Jackson

H. L. JACKSON
Certifying Officer

jc649 U.S. PTO
04/13/99

A/PRDV 99
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Signature

jc541 U.S. PTO
60/129074
04/13/99

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

Docket No.	P32276P		

INVENTOR(s) / APPLICANT(s)

Last Name	First Name	Middle Initial	Residence (City and Either State or Foreign Country)
Storm	Kevin	H.	Britsol, Tennessee, USA

TITLE OF THE INVENTION (280 characters max)

PHARMACEUTICAL FORMULATION

CORRESPONDENCE ADDRESS

SMITHKLINE BEECHAM CORPORATION
Corporate Intellectual Property - UW2220
709 Swedeland Road
King of Prussia

Telephone No. 610-270-5017
Facsimile No. 610-270-5090

State	PA	Zip Code	19406-2799	Country	United States of America

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of Pages	19	☐ Small Entity Statement	
☒ Drawings	Number of Sheets	1	☐ Other (specify)	

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 19-2570	PROVISIONAL FILING FEE AMOUNT ($)	$150.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:_____.

Respectfully submitted,
Signature: Date: 13 April 99

Dara L. Dinner Registration No.: 33,680

o Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

SEND TO: Assistant Commissioner for Patents, Box Provisional Application, Washington, D.C. 20231.

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Pharmaceutical Formulation

This invention relates to novel tablet formulations for oral administration of amoxycillin and potassium clavulanate.

Amoxycillin and potassium clavulanate are respectively a known β-lactam antibiotic and a known β-lactamase inhibitor. Products comprising amoxycillin and potassium clavulanate are marketed under the trade name "Augmentin" by SmithKline Beecham. Such products are particularly effective for treatment of community acquired infections, in particular respiratory tract infections in adults and otitis media in children.

Various tablet formulations of amoxycillin and clavulanate are known, comprising various different weights and ratios of amoxycillin and clavulanate, for instance, conventional swallow tablets comprising 250/125, 500/125, 875/125 and 1000/125mg amoxycillin/clavulanate. Such tablets comprise amoxycillin and clavulanate in the ratio 2:1, 4:1, 7:1 and 8:1. The 875/125 and 1000/125mg tablets were developed to provide tablet formulations which could be administered in a bid (twice daily) dosage regimen.

In addition, WO97/09042 (SmithKline Beecham) describes tablet formulations comprising amoxycillin and clavulanate in a 14:1 ratio. Furthermore, it is suggested that the prefered unit dosage of 1750/125mg may be provided as two tablets, the first comprising 875/125mg amoxycillin and clavulanate and the second 875mg amoxycillin. The 14:1 ratio is said to be useful for the empiric treatment of bacterial infection potentially caused by drug resistant *S pneumoniae* (DRSP).

WO 94/16696 (SmithKline Beecham) discloses generally that clavulanate may unexpectedly enhance the efficacy of amoxycillin against microorganisms having a resistant mechanism which is not β–lactamase mediated.

Existing marketed tablet formulations of amoxycillin and potassium clavulanate are conventional in that they provide immediate release of the active ingredients once the tablet reaches the stomach. There has also been some interest in developing formulations in which the release profile is modified, to allow for a longer interval between dosages, for instances, every 12 hours (bid, q12h), rather than every 8hours (tid, q8h).

Thus, for instance, WO95/20946 (SmithKline Beecham) describes layered tablets comprising amoxycillin and, optionally, clavulanate, having a first layer which is an immediate release layer and a second layer which is a slow release layer. The broadest ratio of amoxycillin to clavulanate is 30:1 to 1:1, with a prefered range of 8:1 to 1:1. Amoxycillin is suitably in the form of amoxycillin trihydrate. Examples provided of such bilayered tablets have amoxycillin trihydrate in the

immediate release layer and amoxycillin plus clavulanate in the slow release layer. Multi-layered tablets are described more generically in WO 94/06416 (Jagotec AG).

In addition, WO95/28148 (SmithKline Beecham) describes amoxycillin/potassium clavulanate tablet formulations having a core containing amoxycillin and potassium clavulanate coated with a release retarding agent and surrounded by an outer casing layer of amoxycillin and potassium clavulanate. The release retarding agent is an enteric coating, so that there is a immediate release of the contents of the outer core, followed by a second phase from the core which is delayed until the core reaches the intestine.

Furthermore, WO96/04908 (SmithKline Beecham) describes amoxycillin/potassium clavulanate tablet formulations which comprise amoxycillin and potassium clavulanate in a matrix, for immediate release, and granules in a delayed release form comprising amoxycillin and potassium clavulanate. Such granules are coated with an enteric coating, so release is delayed until the granules reach the intestine.

In existing tablet formulations, amoxycillin is present in the form amoxycillin trihydrate, as the use of this form provides tablets with greater storage stability than those in which amoxycillin is present as sodium amoxycillin (see GB 2 005 538, Beecham Group Ltd). Sodium amoxycillin is however used as the amoxycillin component in existing formulations of amoxycillin and potassium clavulanate adapted for IV administration. The form of sodium amoxycillin used is a spray-dried form. A further form of sodium amoxycillin, crystalline sodium amoxycillin, is described in EP 0 131 147-A1 (Beecham Group plc). Sodium amoxycillin is relatively water soluble in comparison to amoxycillin trihydrate.

Of concern is the increasing resistance of pathogenic organisms such as those found in respiratory tract infections to anti-infective agents such as amoxycillin/clavulanate. There is a continuing need to provide new formulations of amoxycillin/clavulanate which have improved pharmacokinetic profiles to provide a higher plasma concentration of anti-infective agent. For amoxycillin, it is recognised that that it is necessary to maintain a plasma concentration above the MIC_{90} value of the organism for at least 40% of the interval between dosing. In addition, it is also necessary to provide a plasma C_{max} value well above the MIC_{90} value and it has been suggested that the C_{max} value should be at least three times the MIC_{90} value. It has now been found that an improved pharmacokinetic profile may be achieved by providing the amoxycillin component in two phases.

Accordingly in a first aspect, the present invention provides for a tablet formulation comprising amoxycillin and potassium clavulanate in which all of the

potassium clavulanate and part of the amoxycillin is in a first phase from which it is immediately released and the remainder of the amoxycillin in a second phase from which the amoxycillin is slowly released.

In a further aspect, the present invention provides for a tablet formulation comprising potassium clavulanate and a first part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for immediate release of the potassium clavulanate and amoxycillin and further comprising a second part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for slow release of amoxycillin.

In tablets of the present invention, potassium clavulanate is released substantially immediately from the tablet, when the tablet reaches the stomach and is absorded therefrom, thereby minising the risk of degradation from prolonged exposure to the stomach. The amoxycillin release profile is made up of a contribution from the immediate release component. This is then complemented and extended by an on-going contribution from the slow release component.

As used herein, the term "immediate release" refers to the release of the majority of the active material content within a relatively short time, for example within 1 hour, preferably within 30 minutes, after oral ingestion.

As used herein, the term "slow release" refers to the gradual but continuous release over a relatively extended period of the active material content (in this case amoxycillin) after oral ingestion and which starts when the tablet reaches the stomach and starts to disintegrate/dissolve. The release will continue over a period of time and may continue through until and after the tablet reaches the intestine. This can be contrasted with the term "delayed release" in which release of the active does not start immediately the tablet reaches the stomach but is delayed for a period of time, for instance until when the tablet reaches the intestine when the increasing pH is used to trigger release of the active from the tablet.

The term "amoxycillin" is used generically to refer to both amoxycillin trihydrate and sodium amoxycillin, without distinction.

Unless othewise indicated, weights of amoxycillin and clavulanate refer to the equivalent weights of the coresponding free acids. In addition, it will be appreciated that in practice, weights of amoxycillin and clavulanate to be incorporated into a formulation will be further adjusted, in accord with conventional practice, to take account of the potency of the amoxycillin and clavulanate.

Preferably, the pharmacokinetic profile of tablets of the present invention will provide an amoxycillin C_{max} value in human plasma of at least 12 µg/ml, preferably 16 µg/ml. In addition, tablets of the present invention will preferably

provide a plasma concentration of at least 4 μg/ml of amoxycillin for between 5 and 7h, to support an breakpoint for anti-bacterial activity of at least 4 μg/ml for a dosage interval of 12h, on the basis of providing a plasma concentration of at least 4 μg/ml for at least 40% of the dosing interval. Plasma concentrations of amoxycillin can be readily determined in blood samples taken from patients according to procedures well known and documented in the art.

Preferably, in tablets of the present invention, amoxycillin and potassium clavulanate are present in a ratio by weight of from 1:1 to 30:1, more preferably 10:1 to 20:1, yet more preferably 13:1 to 16:1, typically about 14:1.

In tablets of the present invention, the portion of amoxycillin which is released immediately is provided as amoxycillin trihydrate whilst the portion of amoxycillin which is released slowly is provided as amoxycillin trihydrate or sodium amoxycillin or a mixture thereof. Preferably, amoxycillin is present in the immediate and slow release phases in a ratio of from 3:1 to 1:3, more preferably, from 3:2 to 2:3, typically about 1:1.

A representative tablet of the present invention comprises amoxycillin and potassium clavulanate in a 14:1 ratio, and comprises about 438mg amoxycillin and about 62.5mg of potassium clavulanate in the immediate release phase and about 438mg of amoxycillin in the slow release phase, providing overall an 875/62.5mg tablet.

The immediate and slow release phases may be provided in a number of different formats.

In a preferred aspect, the immediate and slow release phases are provided as separate layers of a layered tablet. Layered tablets comprising amoxycillin and potassium clavulanate have been previously described (WO95/20946 (SmithKline Beecham).

Accordingly, in a further aspect, the present invention provides for a tablet formulation comprising potassium clavulanate and amoxycillin in an immediate release layer phase and amoxycillin in a slow release layer.

An immediate release layer may be, for example, a layer which disintegrates immediately and has a composition similar to that of known tablets which disintegrates immediately. For example, the layer may comprise in addition to the active material content, excipients including binders such as povidone (polyvinylpyrrolidone), for instance the product Plasdone K29-32 (trade mark, ISP, 1361 Alps Road, Wayne, NJ, USA); compression aids; fillers or diluents such as mannitol, microcrystalline cellulose and silicon dioxide, for instance the product Syloid (trade mark); disintegrants such as sodium starch glycollate, for instance the

product Explotab (trade mark, FMC Corp, 1735 market Street, Philadelphia, PA, USA), microcrystalline cellulose, for instance the product Avicel (trade mark, Grace); lubricants such as talc or magnesium stearate; etc. Such a immediate release layer may comprise around 30 - 70 % (all percentages given herein are on a weight percentage basis unless otherwise stated), preferably 50-60% of active material content, around 10 - 30% of fillers/compression aids, and conventional amounts of disintegrants and lubricants etc.

An alternative type of immediate release layer may be a swellable layer having a composition which incorporates polymeric materials which swell immediately and extensively in contact with water or aqueous media, to form a water permeable but relatively large swollen mass. Active material content may be immediately leached out of this mass.

Slow release layers have a composition which comprises amoxycillin together with a release retarding excipient which allows for slow release of amoxycillin. Suitable release retarding excipients include pH sensitive polymers, for instance polymers based upon methacrylic acid copolymers such as the Eudragit (trade mark) polymers, for example Eudragit L (trade mark) which may be used either alone or with a plasticiser; release-retarding polymers which have a high degree of swelling in contact with water or aqueous media such as the stomach contents; polymeric materials which form a gel on contact with water or aqueous media; and polymeric materials which have both swelling and gelling characteristics in contact with water or aqueous media.

Release retarding polymers which have a high degree of swelling include, *inter alia*, cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethylamide, potassium methacrylatedivinylbenzene co-polymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone, high-molecular weight polyvinylalcohols etc.

Release retarding gellable polymers include methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, low-molecular weight polyvinylalcohols, polyoxyethyleneglycols, non-cross linked polyvinylpyrrolidone, xanthan gum etc.

Release retarding polymers simultaneously possessing swelling and gelling properties include medium-viscosity hydroxypropylmethylcellulose and medium-viscosity polyvinylalcohols.

A preferred polymer is xanthan gum, in particular a fine mesh grade of xanthan gum, preferably pharmaceutical grade xanthan gum, 200 mesh, for instance

the product Xantural 75 (also known as Keltrol CR, Trade Mark, Monsanto, 800 N Lindbergh Blvd, St Louis, MO 63167, USA). Xanthan gum is a polysaccharide which upon hydration forms a viscous gel layer around the tablet through which the the active has to diffuse. It has been shown that the smaller the particle size, the slower the release rate. In addition, the rate of release of drug substance is dependent upon the amount of xanthan gum used and can be adjusted to give the desired profile.

Examples of other polymers which may be used include Methocel K4M (Trade Mark), Methocel E5 (Trade Mark), Methocel E5O (Trade Mark), Methocel E4M (Trade Mark), Methocel K15M (Trade Mark) and Methocel K100M (Trade Mark). An example of a suitable polymer mixture is a mixture of Methocel E5 and K4M, for example1:1, w:w.

Other known release-retarding polymers which may be incorporated include hydrocolloids such as natural or synthetic gums, cellulose derivatives other than those listed above, proteinaceous substances such as acacia, gum tragacanth, locust bean gum, guar gum, agar, pectin, carageenam, soluble and insoluble alginates, carboxypolymethylene, gelatin, casein, zein, Veegum (trade mark) and the like.

Such a slow release layer may contain polymers which immediately swell in contact with water or aqueous media so that they form a relatively large swollen mass which is not immediately discharged from the stomach into the intestine.

The slow release layer may also include fillers/compression aids such as microcrystalline cellulose, for instance the product Avicel (trade mark); desiccants, such as silicon dioxide, for instance the product Syloid (trade mark); disintegrants, such as sodium starch glycollate, for instance the product Explotab (trade mark); binders such as povidon (polyvinylpyrrolidone) for instance the product Plasdone K3O (trade mark); lubricants such as talc or magnesium stearate, pH-controlling agents such as potassium dihydrogen phosphate or substantially insoluble ion-exchange resins, and soluble excipients such as mannitol or other soluble sugars.

When xanthan gum is used as release-retarding polymer, the layer contains from 70 to 80% of amoxycillin, from 0.5 to 10%, preferably 1.0 to 6%, more preferably 4 to 5% of xanthan gum, from 10 to 30%, preferably 15 to 30% of fillers/compression aids, and conventional quantities of lubricants. In a preferred embodiment, the slow release layer comprises from 70 to 80% of amoxycillin, from 1.0 to 5%, of xanthan gum, from 15 to 30% of microcrystalline cellulose, and from 0.5 to 1.5% of magnesium stearate.

When release-retarding polymers other than xanthan gum are used, the slow release layer may contain around 30 to 70%, preferably from 40 to 60%, of

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amoxycillin, from 15 to 45% of release-retarding polymer, from 0 to30% of fillers/compression aids, conventional quantities of disintegrants and lubricants, and from 5 - 20% of soluble excipients.

Alternative types of slow-release layers are those in which the active material content is mixed with, coated with, or embedded in, a matrix of a poorly soluble or practically insoluble excipient (e.g. calcium phosphate etc) and/or a hydrophobic excipient (e.g. fats or waxes). Poorly soluble or practically insoluble excipients can yield a very hard tablet which would slowly dissolve or erode from the surface without substantial diffusion of surrounding liquid into the body of the tablet. Hydrophobic excipients similarly hinder moisture ingress and release of active material content occurs through erosion and enzymatic digestion. Examples of such waxes include Compritol (trade mark), for instance, Compritol HD5 and Compritol 888 (trade marks). Compritol wax remains intact in aqueous solutions at all pH, but is digested by lipase enzymes at pH 5-7. Thus active material content such as clavulanate protected with Compritol wax as described above may be released primarily in the small intestine due to the action of intestinal lipase. Typically when the slow- or delayed- release layer includes such a wax, the wax may suitably comprise 10-80% of the layer, e.g. around 20-40%, e.g. 30% ± 5% by weight.

The tablet formulations of the invention may also include one or more barrier layers, which may be located between the respective first and second layers, and/or on one or more of the outer surfaces of the first and second layers, for example the end faces of the layers of a substantially cylindrical tablet. Such barrier layers may, for example, be composed of polymers which are either substantially or completely impermeable to water or aqueous media, or are slowly erodable in water or aqueous media or biological liquids and/or which swell in contact with water or aqueous media. Suitably the barrier layer should be such that it retains these characteristics at least until complete or substantially complete transfer of the active material content to the surrounding medium.

Suitable polymers for the barrier layer include acrylates, methacrylates, copolymers of acrylic acid, celluloses and derivatives for the barrier layer such as ethylcelluloses, cellulose acetate propionate, polyethylenes and polyvinyl alcohols etc. Barrier layers comprising polymers which swell in contact with water or aqueous media may swell to such an extent that the swollen layer forms a relatively large swollen mass, the size of which delays its immediate discharge from the stomach into the intestine. The barrier layer may itself contain active material content, for example the barrier layer may be a slow or delayed release layer. Barrier layers may typically have an individual thickness of 2mm to 10 microns.

Suitable polymers for barrier layers which are relatively impermeable to water include the Methocel (trade mark) series of polymers mentioned above, for example Methocel K100M, Methocel K15M, Methocel E5 and Methocel E50, used singly or combined, or optionally combined with an Ethocel (trade mark) polymer. Such polymers may suitably be used in combination with a plasticiser such as hydrogenated castor oil. The barrier layer may also include conventional binders, fillers, lubricants and compression acids etc such as Polyvidon K30 (trade mark), magnesium stearate, and silicon dioxide, e.g. Syloid 244 (trade mark).

The tablet formulation of the invention may be wholly or partly covered by a coating layer, which may be a protective layer to prevent ingress of moisture, or damage to the tablet. The coating layer may itself contain active material content, and may for example by an immediate release layer, which immediately disintegrates in contact with water or aqueous media to release its active material content, for example amoxycillin and potassium clavulanate.

As well as active material content etc, the tablet of the invention may also include a pH modifying agent, such as a pH buffer, which may be contained in either the immediate-, or slow-release layers, or in a coating around all or part of the tablet. A suitable buffer is calcium hydrogen phosphate.

In a tablet without a barrier layer, the immediate release layer comprises form 50 to 60% and the slow release layer comprises from 40 to 50% of the overall tablet weight.

When a barrier layer is present, the immediate release layer typically comprises from 40 to 50%, the slow release layer comprises from 35 to 45%, and the barrier layer comprises from 5 to 20% of the overall tablet weight.

Suitably the tablet formulations of the invention may be formed by known compression tabletting techniques for example using a known multi-layer tabletting press. Suitably a dry densification process may be used, e.g. briquetting. Typically the active material content, pH modifiers, buffers, fillers and/or diluent, release retarding agents, disintegrants and binders, when used are mixed, then lubricants and compression aids are added. The complete mixture may then be compressed under high pressure in the tablet press. Roller compaction may be used to form granulates for compaction. Alternatively wet granulation may be used, isopropanol being a suitable solvent. A suitable wet granulating aid is Polyvidon K-30 (trade mark).

For making up layers which include a wax, e.g. Compritol (trade mark) dry compression or wet granulation may be used. Typically for wet granulation a colloidal solution or suspension of the wax in a solvent such as dichloromethane may be used. Typically the solution or suspension may be mixed with the layer

ingredients and the wet cake sieved and dried. This can be repeated until the required amount of wax has been incorporated.

The barrier layer may typically be made up by a wet granulation technique, or by dry granulation techniques such as roller compaction. Typically the barrier material, e.g. Methocel (trade mark) is suspended in a solvent such as ethanol containing a granulation acid such as Ethocel or Polyvidon K-30 (trade mark), followed by mixing, sieving and granulation. Typically a first layer may be formed, then a barrier layer deposited upon it, eg by compression, spraying or immersion techniques, then the second layer may be formed so that the barrier layer is sandwiched between the first and second layers. Additionally or alternatively the first and second layers may be formed and a barrier layer may then be formed, eg by compression, spraying or immersion, on one or more of the end faces of the tablet.

Potassium clavulanate is known to be extremely water sensitive. Therefore tablet formulations which contain potassium clavulanate should be made up in dry conditions, preferably at 30% relative humidity or less, and the ingredients of the formulation should be pre-dried where appropriate. Tablet formulations of the invention should be stored in containers which are sealed against the ingress of atmospheric moisture.

The invention also provides a method for the manufacture of a tablet formulation as described above comprising the steps of forming said first and second layers, and any barrier layers and coating layer(s) which may be present.

In addition to the multilayered tablet approach hereinbefore described, other types of tablet may be used to provide an immediate release phase and a slow release phase, using the excipients hereinbefore described but providing the phases in different formats. Thus, the slow release phase may form the core of a tablet which is then surrounded by an outer casing forming the immediate release phase, optionally with an intermediate coating layer around the core and/or a final coating layer around the outer casing (see WO95/28148, SmithKline Beecham). The slow release phase may also be provided as granules which are dispersed in a matrix of amoxycillin and potassium clavulanate, the matrix forming the immediate release phase (see WO96/04908, SmithKline Beecham). In a further variant, a tablet may be prepared from slow release granules comprising amoxycillin and immediate release granules comprising amoxycillin and potassium clavulanate (as described in WO 92/19227, SmithKline Beecham) or immediate release granules comprising amoxycillin and potassium clavulanate, for instance in a 2:1 ratio, and further immediate release granules comprising amoxycillin (as described in WO 98/35672,

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SmithKline Beecham Laboratoires Pharmaceutiques), the granules being combined with extragranular excipients to form tablets.

In a further embodiment, the slow release phase may be provided as a separate tablet, so that the unit dosage is provided as a combination of a conventional tablet in which amoxycillin and potassium clavulanate are released immediately and a tablet comprising amoxycillin (and no potassium clavulanate) from which amoxycillin is released slowly. The weight of potassium clavulanate and the combined weights of amoxycillin in the two tablets will provide the overall unit dosage. Thus, for instance a dosage of 1750/125mg may be provided by an existing 875/125mg tablet (as described in WO 95/28927, SmithKline Beecham) in combination with a slow release tablet comprising 875mg of amoxycillin. Accordingly, in a further aspect, the present invention provides for a kit comprising a conventional (immediate release) tablet comprising amoxycillin and potassium clavulanate and a slow release tablet comprising amoxycillin (and no potassium clavulanate).

Slow release tablets comprising amoxycillin are novel. Accordingly, in a further aspect, the present invention provides for a pharmaceutical tablet comprising amoxycillin (as the sole active ingredient) formulated with a release retarding excipient which cause a slow release of the amoxycillin from the tablet.

Such tablets may comprise from 100 to 1250mg amoxycillin which may be amoxycillin trihydrate or sodium amoxycillin or a mixture thereof, for instance 500, 875 or 1000mg amoxycillin. Suitable excipients for slow release are those hereinbefore described for slow release layers. The tablet may comprise from 0.5 to 10%, preferably from 1 to 6%, more preferably 4 to 5% of xanthan gum.

The invention further provides a formulation as described above for use as a therapeutic substance for oral administration for the treatment of bacterial infections.

The invention further provides for the use amoxycillin and potassium clavulanate as hereinbefore desribed in the manufacture of a medicament for the treatment of bacterial infections.

The invention further provides a method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxycillin and potassium clavulanate included in a formulation as described herein.

Bacterial infections amenable to tablets of the present invention include infections caused by the organisms *S pneumoniae* (including Drug Resistant *S pneumoniae*), *H influenzae* and *M catarrhalis*, such as respiratory tract infections, including sinusitis and bronchitis, where the higher break points achievable through

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the improved pharmacokinetic profile will be especially advantageous compared to existing antibacterial agents.

Tablet formulations according to the present invention may be taken at dosage intervals of 12h. A typical unit dosage comprises 1750/125mg amoxycillin/clavulanate, provided as two tablets each comprising 875/62.5mg amoxycillin/clavulanate.

The invention will now be described by way of example only with reference to the accompanying drawings, in which:

Fig. 1 shows the structure of various types of tablet formulation of the present invention.

Referring to Fig 1, substantially cylindrical compressed tablets of the present invention are shown in longitudinal section. In Fig 1A, the tablet comprises a first layer (1) and a second layer (2), without any barrier layer or coating layer. In Fig 1B, the tablet comprises a first layer (1), a second layer (2), and a barrier layer (3) sandwiched between the first and second layers (1) and (2). In Fig 1C, the tablet comprises a first layer (1), a second layer (2), and a barrier layer (3) located on the end face of the second layer (2). In Fig 1D, the tablet comprises a first layer (1), a second layer (2), a barrier layer (3) sandwiched between the first and second layers (1) and (2), and a coating layer (4) which partly covers the tablet. The dotted line shows the possibility of the coating layer (4A) covering the entire tablet. In Fig. 1E, the tablet comprises a first layer (1) a second layer (2), and a third layer (3) intermediate between the first and second layers (1) and (2). All three of these layers (1), (2) and (3) include active material content.

Formulations for an amoxycillin slow release tablet

875 mg Crystalline Sodium Amoxicillin Tablets with Xanthan Gum, 200 mesh.

	mg/tablet	%	mg/tablet	%
Crystalline Sodium Amoxicillin 91%*	961.54	73.96	961.54	73.96
Dried Microcrystalline Cellulose NF	305.96	23.54	273.46	21.04
Magnesium Stearate NF	13.0	1.00	13.0	1.00
xanthan gum 200 mesh**	19.5	1.50	52.0	4.00
Total	1300	100 Total	1300	100

875 mg Amoxicillin Trihydrate Tablets with Xanthan Gum, 200 mesh

	mg/tablet	%	mg/tablet	%
Amoxicillin Trihydrate 86%*	1017.4	78.26	1017.4	78.26
Dried Microcrystalline Cellulose NF	250.1	19.24	217.6	16.74
Magnesium Stearate NF	13.0	1.00	13.0	1.00
Xanthan Gum, 200 mesh**	19.5	1.50	52.0	4.00
Total	1300	100 Total	1300	100

* adjusted for the potency of the amoxycillin component and corresponding to 875mg amoxycillin,

** Xantural 75

Slow release layers may be formed using half the quantities given above, for a slow release layer comprising about 438mg amoxycillin.

Immediate release layer - 1

Amoxycillin trihydrate	507mg
(equiv to amoxycillin free acid)	(438)
Potassium clavulanate	71.8
(equivalent to clavulanic acid)	(62.5)
Microcrystalline cellulose (Avicel PH102)	125
Sodium starch glycollate (Explotab)	26
Magnesium stearate	6.5

The immediate release layer comprises nominally 438/62.5mg amoxycillin/clavulnate.

Immediate release layer - 2

Amoxycillin trihydrate	507mg
(equiv to amoxycillin free acid)	(438)
Potassium clavulanate	71.8
(equivalent to clavulanic acid)	(62.5)
Microcrystalline cellulose (Avicel PH102)	135
Sodium starch glycollate (Explotab)	34
Talc	67
Magnesium stearate	25
Silica (Syloid)	17

The immediate release layer comprises nominally 438/62.5mg amoxycillin/clavulnate.

Barrier Layers

Barier layers and methods for their preparation are described in WO 95/20946 (SmithKline Beecham).

Preparation of Tablets

The active ingredients, fillers and diluents (mannitol), release controlling agents or disintegrants (Avicel, Explotab) and binders (Plasdone K29-32) are mixed during 5 minutes in a Stefan Mixer at speed level 11. Lubricants (talc, Mg-stearate) and colloidal silicon dioxide (Syloid 244) are added, and mixing at level 1 is continued for another minute. The complete mixture is slugged on a Kilian tablet press (briquetting step), followed by size reduction (Frewitt) and passage through an oscillatory 1 mm sieve. If the flow properties are unsatisfactory, the briquetting step iss repeated.

In some cases, where the bulk density is rather low, a densifying step (pre-tabletting and sieving as in the briquetting method) may be required in order to achieve the nominal weight of a particular layer.

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Dissolution Testing Methods

The release of amoxycillin and clavulanate from tablets into static media may be measured using the USP Dissolution Test Method II.

The release of amoxycillin and clavulanate from tablets into flowing water and other media may be measured using the USP Method IV Dissolution , using large (22.6 mm, 8.3 ml/min) and small (12 mm 8.3 ml/min) cells.

The test was performed according to USP XXXII <724>, apparatus 4.

Dissolution apparatus:

Dissolution apparatus:	SOTAX CE6 flow cell
	SOTAX CY7-50 pump

Test specifications:

Temperature:	37.0 ± 0.5°C
Test medium:	0 - 2h: HCl 0.01 M (pH 2.0)
	2 - 8h: phosphate buffer 0,05 M; pH = 6.6
Flow rate:	8.3 ml/min (500 ml/h)
Flow cell:	22.6 mm diameter

Solutions:

- 0.05 M phosphate buffer solution 3 (pH 6.6): Dissolve 544g potassium dihydrogenphosphate in 20.0L water and adjust to pH 6.6 with NaOH 40% (m/v).
- 0.05 M phosphate buffer solution 4 (pH 6.6): Dissolve 408g potassium dihydrogenphosphate and 39g sodium hydroxide pellets p.a. in 60L water.

Method:

A tablet may be tested each as follows. A 5 mm diameter ruby bead is placed at the bottom of the cone of the flow cell and the cone is filled with 1 mm diameter glass beads. A tablet is introduced into the cell and fixed vertically using a holder. The filter head is assembled and the parts fixed together by means of a clamping device. The dissolution medium warmed to 37.0 ± 0.5°C is introduced through the bottom of the cell at a flow rate of 8.3 ml/min. Hydrochloric acid (0.01 M) is used from the beginning for 2 hours and then changed to buffer solution 4 until the end of the run.

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The drug release after 30 min, 60 min 2 h 3 h, 4 h, 5 h, 6 h, 7 h and 8 h is determined.

As potassium clavulanate is very unstable at low pH values, the fractions for the time from 0 to 2 hours (medium = 0.01 M HCL) are collected directly in a buffer solution and mixed well with this buffer in a ratio of about 1:1.

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Claims:

1. A tablet formulation comprising amoxycillin and potassium clavulanate in which all of the potassium clavulanate and part of the amoxycillin is in a first phase from which it is immediately released and the remainder of the amoxycillin in a second phase from which the amoxycillin is slowly released.

2. A tablet formulation comprising potassium clavulanate and a first part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for immediate release of the potassium clavulanate and amoxycillin and further comprising a second part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for slow release of amoxycillin.

3. A tablet formulation as claimed in claim 1 in which the pharmacokinetic profile of the tablets will provide an amoxycillin C_{max} value in human plasma of at least 12 μg/ml.

4. A tablet as claimed in claim 1 in which pharmacokinetic profile of the tablets will provide an amoxycillin plasma concentration of at least 4 μg/ml for between 5 and 7h.

5. A tablet formulation as claimed in claim 1 in which amoxycillin and potassium clavulanate are present in a ratio by weight of from 1:1 to 30:1,

6. A tablet formulation as claimed in claim 5 in which amoxycillin and potassium clavulanate are present in a ratio by weight of 10:1 to 20:1.

7. A tablet formulation as claimed in claim 5 in which amoxycillin and potassium clavulanate are present in a ratio by weight of 13:1 to 16:1.

8. A tablet formulation as claimed in claim 5 in which amoxycillin and potassium clavulanate are present in a ratio by weight of about 14:1.

9. A tablet formulation as claimed in claim 1 in which the portion of amoxycillin which is released immediately is provided as amoxycillin trihydrate whilst the portion of amoxycillin which is released slowly is provided as amoxycillin trihydrate or sodium amoxycillin or a mixture thereof.

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19. A tablet formulation as claimed in claim 18 in which the xanthan gum is a fine mesh grade of xanthan gum.

20. A tablet formulation as claimed in claim 19 in which the xanthan gum is pharmaceutical grade xanthan gum, 200 mesh.

21. A tablet formulation as claimed in claim 18 in which the xanthan gum is present in from from 0.5 to 10% by weight of the layer.

22. A tablet formulation as claimed in claim 14 in which the slow release layer comprises from 70 to 80% of amoxycillin, from 0.5 to 10% of xanthan gum, from 10 to 30% of fillers/compression aids, and conventional quantities of lubricants.

23. A tablet formulation as claimed in claim 22 in which the slow release layer comprises from 70 to 80% of amoxycillin, from 1.0 to 6%, of xanthan gum, from 15 to 30% of microcrystalline cellulose, and from 0.5 to 1.5% of magnesium stearate.

24. A kit comprising an immediate release tablet comprising amoxycillin and potassium clavulanate and a slow release tablet comprising amoxycillin (and no potssium clavulanate).

25. A pharmaceutical tablet comprising amoxycillin (as the sole active ingredient) formulated with a release retarding excipient which cause a slow release of the amoxycillin from the tablet.

26. A tablet as claimed in claim 25 which comprises 100 to 1250mg amoxycillin.

27. A tablet as claimed in claim 25 in which the release retarding excipient is xanthan gum.

28. A tablet formulation as claimed in claim 25 in which the xanthan gum is pharmaceutical grade xanthan gum, 200 mesh.

29. A tablet formulation as claimed in claim 25 in which the xanthan gum is present in from from 0.5 to 10% by weight of the layer.

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30. A a method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxycillin and potassium clavulanate in a tablet formulation comprising a first phase in which all of the potassium clavulanate and part of the amoxycillin is immediately released and a second phase comprising the remainder of the amoxycillin from which the amoxycillin is slowly released

31. A method as claimed in claim 30 in which the infection is caused by the organisms *S pneumoniae* (including Drug Resistant *S pneumoniae*), *H influenzae* and/or *M catarrhalis*.

32. A method as claimed in claim 30 in which the tablet formulation is taken at dosage intervals of 12h.

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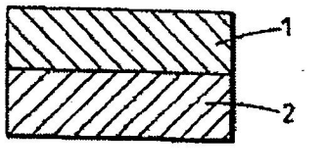


Fig. 1A

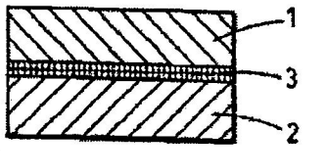


Fig. 1B

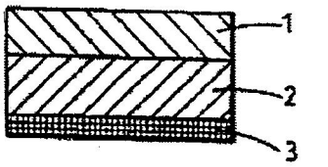


Fig. 1C

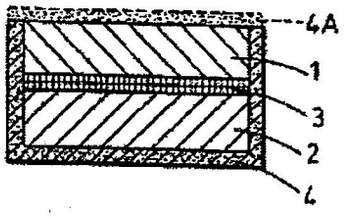


Fig. 1D

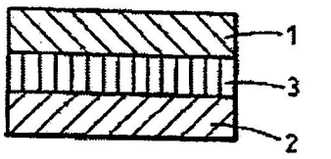


Fig. 1E

Reivindicaciones

1. Un método para tratar infecciones bacterianas en seres humanos que comprende la administración a los mismos de una cantidad terapéuticamente efectiva de amoxicilina y clavulanato de potasio de manera que la cantidad de amoxicilina se encuentra en el rango de 1.900 a 2.600 miligramos y la cantidad de clavulanato de potasio es tal que la proporción de peso de la amoxicilina al clavulanato es de 1:14 a 1:20, a intervalos de unas 12 horas.

2. Un método como el de la reivindicación 1 en el que el régimen de dosificación proporciona una concentración media en plasma de amoxicilina de 4 μg/mL durante por lo menos 4,4 horas y una concentración media máxima en plasma (C_{max}) de amoxicilina de por lo menos 12 μg/mL.

3. Un método como el de la reivindicación 2 en el que el régimen de dosificación proporciona una concentración media en plasma de amoxicilina de 4 μg/mL durante por lo menos 4,8 horas y una concentración máxima media en plasma (C_{max}) de amoxicilina de por lo menos 16 μg/mL.

4. Un método como el de la reivindicación 1 en el que el régimen de dosificación proporciona una concentración media en plasma de amoxicilina de 8 μg/mL durante por lo menos 4,4 horas.

5. Un método como el de la reivindicación 1 en el que la dosificación proviene de una formulación de liberación inmediata.

6. Un método como el de la reivindicación 5 en el que la dosificación es 2.000/125, 2.250/125 o 2.500/125 mg de amoxicilina y clavulanato de potasio, respectivamente.

7. Un método como el de la reivindicación 6 en el que la dosificación

se suministra como una sola tableta, o como un número de tabletas más pequeñas, algunas de las cuales pueden ser las mismas y otras pueden contener solo amoxicilina y no clavulanato de potasio.

8. Un método como el de la reivindicación 1 en el que la dosificación proviene de una formulación de liberación modificada.

9. Un método como el de la reivindicación 8 en el que la dosificación se suministra como un número de tabletas, algunas de las cuales pueden ser las mismas y otras pueden contener solo amoxicilina y no clavulanato de potasio.

10. Un método como el que se presenta en la reivindicación 8 en el que la dosificación es 2.000/125 mg de amoxicilina y clavulanato de potasio.

11. Un método para tratar infecciones bacterianas en humanos que comprende la administración de una cantidad terapéuticamente efectiva de amoxicilina y clavulanato de potasio de manera que la cantidad de amoxicilina se encuentre el el rango de 1.400 a 1.900 mg, preferiblemente de 1.500 a 1.900 mg, y una cantidad de clavulanato de potasio que la proporción de peso de la amoxicilina al clavulanato sea de 1:12 a 1:14, a intervalos de unas 12 horas, de tal manera que el régimen de dosificación proporciona una concentración media en plasma de amoxicilina de 4μg/mL durante por lo menos 4,4 horas y una concentración máxima media en plasma (Cmax) de amoxicilina de por lo menos 12 μg/mL.

12. Un método como el de la reivindicación 11 en el cual el régimen de dosificación proporciona una concentración media en plasma de amoxicilina de 4μg/mL durante por lo menos 4,8 horas y una concentración máxima media en plasma (Cmax) de amoxicilina de por lo menos 16 μg/mL.

13. Un método como el de la reivindicación 11 en el cual la dosificación proviene de una formulación de liberación modificada.

14. Un método como el de la reivindicación 13 en el cual la dosificación es 1.500/125 ó 1.750/125 mg de amoxicilina y clavulanato de potasio.

15. Un método como el de la reivindicación 1 en el cual la infección es causada por los organismos *S pneumoniae* (incluida la *S pneumoniae* resistente a los medicamentos y a la penicilina), *H influenzae* y/o *M catarrhalis*.

16. Una formulación farmacéutica de tableta de liberación inmediata que contiene 1.000 mg ±5% de amoxicilina y 62.5 mg ±5% de clavulanato de potasio, en una proporción nominal de aproximadamente 16:1, en combinación con excipientes o portadores farmacéuticamente aceptables.

17. Una formulación farmacéutica de liberación inmediata en forma de una sola dosis en sobre que contiene 2.000, 2.250 ó 2500 mg ±5% de amoxicilina y 125 mg ±5% de clavulanato de potasio, en una proporción nominal de unos 16:1, 18:1 ó 20:1, respectivamente, o las cantidades por mitad de los mismos, en combinación con excipientes o portadores farmacéuticamente aceptables.

18. Una tableta masticable de liberación inmediata, opcionalmente efervescente, que contiene 2.000, 2.250 ó 2.500 mg de amoxicilina y 125 mg ±5% de clavulanato de potasio en una proporción nominal de aproximadamente 16:1, 18:1 ó 20:1 respectivamente, o la correspondiente mitad de las cantidades de la misma, en combinación con una base masticable y, en caso de ser efervescente, con un efervescente combinado con otros excipientes o portadores farmacéuticamente aceptables.

19. Una formulación farmacéutica de liberación modificada que contiene amoxicilina y clavulanato de potasio en la que todo el clavulanato de potasio y una primera parte de la amoxicilina son formulados con excipientes farmacéuticamente aceptables que permiten la liberación inmediata del clavulanato de potasio y la primera parte de amoxicilina, para formar una fase de liberación inmediata, y que además comprende una segunda parte de amoxicilina formulada con excipientes framacéuticamente aceptables que permiten la liberación lenta de la segunda parte de la amoxicilina para formar una fase de liberación lenta.

20. Una formulación de liberación modificada como la de la reivindicación 19,

que tiene un perfil bifásico con respecto a la amoxicilina.

21. Una formulación de liberación modificada como la de la reivindicación 19 que tiene un valor AUC que es por lo menos el 80% de aquel de la dosificación correspondiente de amoxicilina tomada como una(s) tableta(s) de dosificación convencional (liberación inmediata), por el mismo período de dosificación.

22. Una formulación farmacéutica como la de la reivindicación 19 en la cual la proporción de amoxicilina en las fases de liberación inmediata y lenta es de 3:1 a 1:3.

23. Una formulación farmacéutica como la de la reivindicación 19 que comprende una dosis unitaria en el rango de 700 a 1.300 mg. Preferiblemente, 950 a 1.300 mg, de amoxicilina y la cantidad correspondiente de clavulanato de potasio.

24. Una formulación farmacéutica como la de la reivindicación 23 en la que la dosis unitaria es 1.000, 875 ó 750 mg ±5% de amoxicilina y 62.5 mg ±5% de clavulanato de potasio, en una proporción nominal de aproximadamente 16:1, 14:1 ó 12:1, respectivamente, en combinación con excipientes o portadores farmacéuticamente aceptables.

25. Una formulación farmacéutica como la de la reivindicación 24 que es una formulación de tableta.

26. Una tableta farmacéutica como la de la reivindicación 25 que contiene 1.000 mg ±5% de amoxicilina y 62.5 mg ±5% de clavulanato de potasio, en una proporción nominal de aproximadamente 16:1 en la cual la fase de liberación inmediata contiene unos 563 mg ±5% de amoxicilina y unos 62.5 mg ±5% de clavulanato de potasio y la fase de liberación lenta que contiene unos 438 mg ±5% de amoxicilina.

27. Una formulación farmacéutica como la de la reivindicación 19 en la cual la amoxicilina de la fase de liberación lenta consiste básicamente en amoxicilina cristalina de sodio.

28. Una formulación farmacéutica como la de la reivindicación 19 que es una

tableta de capas y en la cual las fases de liberación inmediata y lenta son provistas como capas separadas de tabletas en capas.

29. Una formulación de tableta como la de la reivindicación 28 en la cual la capa de liberación lenta contiene un excipiente retardante de liberación que se selecciona de polímeros sensibles al pH; un polímero retardante de liberación con un alto grado de expansión cuando entra en contacto con agua o un medio acuoso; un material polimérico que forma un gel al entrar en contacto con agua o un medio acuoso; y un material polimérico que tiene ambas características, que se expande y se gelifica cuando entra en contacto con agua o un medio acuoso.

30. Una formulación de tableta como la de la reivindicación 29 en la cual el polímero retardante de liberación que se gelifica es seleccionado de metilcelulosa, carboximetilcelulosa, hidroxipropilmetilcelulosa de bajo peso molecular, polivinilalcoholes de bajo peso molecular, polioxietilenoglicoles, polivinilpirrolidona sin enlaces cruzados o goma arábiga.

31. Una formulación de tableta como la de la reivindicación 29 en la cual el excipiente retardante de liberación es goma arábiga.

32. Una formulación de tableta como la de la reivindicación 31 en la que la goma arábiga está presente en de 1 a 25% por peso de la capa.

33. Una formulación de tableta como la de la reivindicación 28 en la cual la capa de liberación lenta contiene de 70 a 80% de amoxicilina, de 1 a 25% de goma arábiga, de 10 a 20% de materiales que ayudan a rellenar y comprimir, y cantidades convencionales de lubricantes.

34. Una formulación de tableta como la de la reivindicación 28 en la cual la fase de liberación lenta contiene amoxicilina de sodio y en la cual el excipiente retardante de liberación es un ácido orgánico farmacéuticamente aceptable presente en una proporción molar de 100:1 a 1:10 (sal de amoxicilina a ácido orgánico).

35. Una formulación de tableta como la de la reivindicación 34 en la cual el

ácido farmacéuticamente aceptable es ácido cítrico presente en una proporcion molar de aproximadamente 50:1 a 1:2.

36. Una formulación de tableta como la de la reivindicación 35 que contiene además un polímero retardante de liberación que se gelifica.

37. Una formulación de tableta como la de la reivindicación 36 en la que el polímero retardante de liberación que se gelifica es goma arábiga.

38. Una formulación de tableta como la de la reivindicación 36 en la que la goma arábiga está presente en de 0,5 a 8% por peso de la capa de liberación lenta.

39. Una formulación de tableta como la de la reivindicación 34 que contiene 1.000 mg ±5% de amoxicilina y 62.5 mg ±5% de clavulanato de potasio y que contiene en la capa de liberación lenta unos 438 mg ±5% de amoxicilina de sodio cristalina, unos 78 mg ±10% de ácido cítrico y aproximadamente 2% por peso de goma arábiga.

40. Una formulación farmacéutica como la de la reivindicación 19 formada por gránulos de liberación lenta que contienen amoxicilina y gránulos de liberación inmediata que contienen amoxicilina y clavulanato de potasio o gránulos de liberación inmediata que contienen amoxicilina y clavulanato de potasio y además gránulos de liberación inmediata que contienen amoxicilina.

41. Un método para tratar infecciones bacterianas en seres humanos que comprende la administración de una dosificación de amoxicilina y clavulanato de potasio que contiene nominalmente unos 2.000 mg ±5% de amoxicilina y nominalmente unos 125 mg ±5% de clavulanato de potasio, dos veces al día.

42. Una formulación farmacéutica que contiene 1.000 mg ±5% de amoxicilina y 62.5 mg ±5% de ácido clavulánico de potasio, en una proporción nominal de unos 16:1, en combinación con excipientes o portadores farmacéuticamente aceptables.

43. Una formulación como la de la reivindicación 42 en la cual la amoxicilina

está presente como una mezcla de trihidrato de amoxicilina y amoxicilina de sodio en una proporción de 3:1 a 1:3.

44. Una formulación farmacéutica que contiene amoxicilina y clavulanato de potasio en una proporción de 1:1 a 30:1 en la cual la amoxicilina es provista como una mezcla de trihidrato de amoxicilina y amoxicilina de sodio en una proporción de 3:1 a 1:3.

45. Una formulación farmacéutica como la de la reivindicación 44 en la cual la proporción de trihidrato de amoxicilina y amoxicilina de sodio va de 3:2 a 2:3.

46. Una formulación farmacéutica que contiene una sal de amoxicilina soluble aceptable farmacéuticamente, en una fase de liberación lenta que además contiene un excipiente retardante de liberación que es un ácido orgánico farmacéuticamente aceptable presente en una proporción molar de 100:1 a 1:10 (sal de amoxicilina a ácido orgánico).

47. Una formulación farmacéutica como la de la reivindicación 46 en la cual la proporción molar es de 50:1 a 1:5.

48. Una formulación farmacéutica como la de la reivindicación 46 en la cual el ácido orgánico es acido cítrico.

49. Una formulación farmacéutica como la de la reivindicación 46 en la cual la sal soluble de amoxicilina es amoxicilina de sodio.

50. Un juego que comprendee una tableta para liberación inmediata que contiene amoxicilina y clavulanato de potasio, opcionalmente con una tableta convencional (de liberación inmediata) que contiene amoxicilina, y una tableta de liberación lenta que contiene amoxicilina (pero sin clavulanato de potasio).

51. Una tableta farmacéutica que contiene amoxicilina (como único ingrediente activo) formulada con un excipiente retardante de liberación que ocasiona una liberación lenta de la amoxicilina desde la tableta, y excluye las tabletas que contienen trihidrato de amoxicilina de 400 a 500mg. O una mezcla que contiene por lo menos un 70% de trihidrato de amoxicilina y hasta un 30% de amoxicilina de sodio e hidroxipropil metilcelulosa.

52. Una tableta como la de la reivindicación 51 que contiene de 100 a 1.250 mg de amoxicilina.

53. Una tableta como la de la reivindicación 51 en la cual el excipiente retardante de liberación es goma arábiga.

54. Una formulación de tableta como la de la reivindicación 51 en la cual la goma arábiga es una goma arábiga de grado farmacéutico malla 200.

55. Una formulación de tableta como la de la reivindicación 51 en la cual la goma arábiga está presente desde 0,5 a 25% por peso.

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APPLICATION NUMBER: ***60/159,813***
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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

Docket No.	P32443P		

INVENTOR(s) / APPLICANT(s)

Last Name	First Name	Middle Initial	Residence (City and Either State or Foreign Country)
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TITLE OF THE INVENTION (280 characters max)

Novel Method of Treatment

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of Pages	36	☐ Small Entity Statement	
☒ Drawings	Number of Sheets	3	☐ Other (specify)	

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. **19-2570**	PROVISIONAL FILING FEE AMOUNT ($)	**$150.00**

Respectfully submitted,
Signature:
Dara L. Dinner

Date: 15 Oct. 99
Registration No.: 33,680

☐ Additional inventors are being named on separately numbered sheets attached hereto.

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Novel Method of Treatment

Field of the Invention

This invention relates to a novel method of treatment using amoxycillin and potassium clavulanate and for novel formulations, in particular tablet formulations for use in such methods.

Background of the Invention

Amoxycillin and potassium clavulanate are respectively a known β-lactam antibiotic and a known β-lactamase inhibitor. Products comprising amoxycillin and potassium clavulanate are marketed under the trade name "Augmentin" by SmithKline Beecham. Such products are particularly effective for treatment of community acquired infections, in particular respiratory tract infections in adults and otitis media in children.

Various tablet formulations of amoxycillin and clavulanate have been approved for marketing, comprising various different weights and ratios of amoxycillin and clavulanate, for instance, conventional swallow tablets comprising 250/125, 500/125, 500/62.5, and 875/125 mg amoxycillin/clavulanate. Such tablets comprise amoxycillin and clavulanate in the ratio 2:1, 4:1, 8:1 and 7:1, respectively . The 875/125 mg tablet was developed to provide a tablet formulation which could be administered in a bid (twice daily) dosage regimen It is also marketed for tid (three times daily) dosing, in Italy and Spain. The 500/62.5 mg tablet was also developed to provide a tablet formulation which could be administered in a bid dosage regimen, two such tablets being taken every 12h, in preference to a single 1000/125 mg tablet. A 1000/125mg single dosage is also available, in France, but as a single dosage sachet rather than a tablet.

In addition, WO 97/09042 (SmithKline Beecham) describes tablet formulations comprising amoxycillin and clavulanate in a ratio in the range 12:1 to 16:1, preferably 14:1. Furthermore, it is suggested that the preferred unit dosage of 1750/125mg may be provided as two tablets, the first comprising 875/125mg amoxycillin and clavulanate and the second 875 mg amoxycillin. The 14:1 ratio is said to be useful for the empiric treatment of bacterial infection potentially caused by drug resistant *S pneumoniae* (DRSP). This patent application also describes paediatric formulations comprising amoxycillin and clavulanate in a 14:1 ratio, for administering amoxycillin dosages of 90 mg/kg/day. Data suggest that such a

dosage may provide antibiotic concentrations sufficient to eradicate DRSP with MICs ≤ 4 μg/ml (Bottenfield et al, Pediatr Infect Dis J, 1998, 17, 963-8).

WO 94/16696 (SmithKline Beecham) discloses generally that clavulanate may unexpectedly enhance the efficacy of amoxycillin against microorganisms having a resistant mechanism which is not β–lactamase mediated.

It has been determined that there is a continuing need to provide new dosage regimens for amoxycillin/clavulanate which are effective against more resistant bacteria.

Summary of the Invention

The present invention releates to a method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxycillin and potassium clavulanate such that the amount of amoxycillin is in the range 1900 to 2600 mg and the amount of potassium clavulanate is such that the weight ratio of amoxycillin to clavulanate is from 1:14 to 1:20, at intervals of about 12 hours. Suitably, the infection is caused by the organisms *S pneumoniae* (including Drug Resistant and Penicillin Resistant *S pneumoniae*), *H influenzae* and/or *M catarrhalis*.

The present invention also relates to an immediate release pharmaceutical tablet formulation comprising 1000 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanate, in a nominal ratio of about 16:1, in combination with pharmaceutically acceptable excipients or carriers.

The present invention also relates to an immediate release pharmaceutical formulation in the form of a single dose sachet comprising 2000, 2250 or 2500 mg ±5% amoxycillin and 125 mg ±5% potassium clavulanate, in a nominal ratio of about 16:1, 18:1 or 20:1, respectively, or the corresponding half quantities thereof, in combination with pharmaceutically acceptable excipients or carriers.

Other suitable modified or immediate release formulaions are described herein in greater detail.

Brief Description of the Drawings

Figure 1 shows the structure of various types of layered tablets of the present invention, in particular the structure of substantially cylindrical compressed tablets are shown in longitudinal section. In

Fig 1A, shows a tablet comprising a first layer (1) and a second layer (2), without any barrier layer or coating layer.

Fig 1B, shows a tablet comprising a first layer (1), a second layer (2), and a barrier layer (3) sandwiched between the first and second layers (1) and (2).

Fig 1C, shows a tablet comprising a first layer (1), a second layer (2), and a barrier layer (3) located on the end face of the second layer (2).

Fig 1D, shows a tablet comprising a first layer (1), a second layer (2), a barrier layer (3) sandwiched between the first and second layers (1) and (2), and a coating layer (4) which partly covers the tablet. The dotted line shows the possibility of the coating layer (4A) covering the entire tablet.

Fig. 1E, shows a tablet comprising a first layer (1) a second layer (2), and a third layer (3) intermediate between the first and second layers (1) and (2). All three of these layers (1), (2) and (3) include active material content.

Figure 2 demonstrates the pharmacokinetic profile of Study A.

Figure 3 demonstrates the pharmacokinetic profile for amoxycillin plasma concentration (in which A is formulation V, B is formulation VI, D is formulation VIII).

Detailed Description of the Invention

Existing marketed tablet formulations of amoxycillin and potassium clavulanate are conventional in that they provide immediate release of the active ingredients once the tablet reaches the stomach. There has also been some interest in developing formulations in which the release profile is modified, to allow for a longer interval between dosages, for instances, every 12 hours (bid, q12h), rather than every 8 hours (tid, q8h).

Thus, for instance, WO 95/20946 (SmithKline Beecham) describes layered tablets comprising amoxycillin and, optionally, clavulanate, having a first layer which is an immediate release layer and a second layer which is a slow release layer. The broadest ratio of amoxycillin to clavulanate is 30:1 to 1:1, with a preferred range of 8:1 to 1:1. Amoxycillin is suitably in the form of amoxycillin trihydrate. Examples provided of such bilayered tablets have amoxycillin trihydrate in the immediate release layer and amoxycillin plus clavulanate in the slow release layer. Multi-layered tablets are described more generically in WO 94/06416 (Jagotec AG).

In addition, WO 95/28148 (SmithKline Beecham) describes amoxycillin/potassium clavulanate tablet formulations having a core containing amoxycillin and potassium clavulanate coated with a release retarding agent and surrounded by an outer casing layer of amoxycillin and potassium clavulanate. The release retarding agent is an enteric coating, so that there is a immediate release of the contents of the outer core, followed by a second phase from the core which is

delayed until the core reaches the intestine. Furthermore, WO 96/04908 (SmithKline Beecham) describes amoxycillin/potassium clavulanate tablet formulations which comprise amoxycillin and potassium clavulanate in a matrix, for immediate release, and granules in a delayed release form comprising amoxycillin and potassium clavulanate. Such granules are coated with an enteric coating, so release is delayed until the granules reach the intestine. WO 96/04908 (SmithKline Beecham) describes amoxycillin/potassium clavulanate delayed or sustained release formulations formed form granules which have a core comprising amoxycillin and clavulanate, surrounded by a layer comprising amoxycillin. WO 94/27557 (SmithKline Beecham) describes controlled release formulations of amoxycillin and clavulanic acid prepared using a hydrophobic waxy material which is then subjected to thermal infusion.

Controlled release formulation comprising amoxycillin has been described by Hoffman *et al*, (Journal of Controlled Release, 1998, 54, 29-37 and WO 98/22091) and Hilton et al (Journal of Pharmaceutical Sciences, 1993, 82, 737-743). Hoffman et al describe a tablet comprising 500 mg of amoxycillin in a matrix comprising hydroxypropyl methyl cellulose, designed to release 50% of its contents in the first three hours and complete the drug release process over eight hours. The time above MIC was found to be significantly extended, compared to a capsule formulation, but not enough for a 12 h dosing interval. The discussion is in the context of a theoretical MIC of 0.2 µg/ml. In contrast, Hilton *et al* described a 750 mg controlled release tablet but failed to show any advantage over a conventional capsule, in particular the bioavailability was reduced to 64.6% compared with the same dosage provided in a capsule . Part of the challenge in providing formulations of amoxycillin in which the drug release is effectively modified is the relatively narrow window for absorption of the drug in the small intestine and the relatively short half life of the drug.

Controlled release formulations comprising from 7.5 to 25% xanthan gum are described in EP 0 234 670-A (Boots Co plc). The preferred embodiment is a tablet comprising ibuprofen as the drug substance and 15-20% xanthan gum, which is taken once daily.

In existing tablet formulations, amoxycillin is present in the form amoxycillin trihydrate, as the use of this form provides tablets with greater storage stability than those in which amoxycillin is present as sodium amoxycillin (see GB 2 005 538, Beecham Group Ltd). Sodium amoxycillin is however used as the amoxycillin component in existing formulations of amoxycillin and potassium clavulanate adapted for IV administration. The form of sodium amoxycillin used is

a spray-dried form. A further form of sodium amoxycillin, crystalline sodium amoxycillin, is described in EP 0 131 147-A1 (Beecham Group plc). Sodium amoxycillin is relatively water soluble in comparison to amoxycillin trihydrate.

Formulations comprising clavulanic acid and a pharmaceutically acceptable organic acid or a salt-like thereof, for example calcium citrate, have been described in WO 96/07408 (SmithKline Beecham). In such formulations, it was postulated that the presence of the calcium citrate would help suppress the gastro-intestinal intolerance associated with oral dosing of clavulanate-containing products.

Furthermore, US patent no. 5 051 262 (Elan Corp) describes the incorporation of an organic acid into a modified release formulation, to provide a microenvironment in which the locally modified pH helps to protect the active ingredient from degradation.

Of concern is the increasing resistance of pathogenic organisms, such as those found in respiratory tract infections, to anti-infective agents such as amoxycillin/clavulanate, in particular drug resistant *S pneumoniae*. Increased resistance to penicillin of *S pneumoniae* (due to penicillin binding proteins) is developing around the world and is affecting clinical outcomes (see for instance Applebaum P C, Ped Inf Dis J, 1996, 15(10), 932-9). These resistant *S pneumoniae* have been termed "DRSP" as they often exhibit decreased susceptibility across a wide range of antimicrobial classes, including macrolides, azalides, beta-lactams, sulfonamides and tetracyclines. Amoxycillin (with or without clavulanate), along with some of the newer quinolones, has remained among the most active oral drugs against the increasingly resistant isolates of *S pneumoniae*, based on both MIC levels and pharmacokinetic properties of these compounds. Resistance rates (and MICs) have however continued to increase. Susceptible *S pneumoniae* have an MIC of ≤ 2 µg/ml, Intermediate resistance is been defined as an MIC in the range 0.12 to 1.0 µg/ml whilst Penicillin resistance is defined as an MIC of ≥ 2 µg/ml. There is a consequently a need to provide new formulations of amoxycillin/clavulanate that combine the known safety profile and broad spectrum with improved activity against DRSP with higher MICs in empiric therapy settings where *H influenzae* and *M catarrhalis* can be anticipated to be co-pathogens..

For β–lactams, including amoxycillin, it is recognised time above minimum inhibitory concentration (T > MIC) is the pharmacodynamic parameter most closely related to efficacy. For a variety of β–lactams, a bacteriological cure rate of 85 to 100% is achieved when serum concentrations exceed the MIC for more than about 40% of the dosing interval (Craig and Andes, Ped Inf Dis J, 1996, 15, 255-259). For a 12 hour dosing interval, this is about 4.8 hours. In addition, it is also necessary to

provide a plasma C_{max} value well above the MIC value and it has been suggested that the C_{max} value should be at least three times, if not four times, the MIC value.

In a clinical study using the existing Augmentin 875/125mg tablet, it was found that, when dosed at 12 hour intervals, the time above MIC was about 40% for an MIC of 2 μg/ml but only about 30% for an MIC of 4 μg/ml. The existing Augmentin 875/125mg tablet has a C_{max} value of 11.6±2.8 μg/ml (Physicians Desk Reference, Medical Economics Co, 52 edition, 1998, 2802).

Accordingly, in a first aspect, the present invention provides for a method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxycillin and potassium clavulanate such that the amount of amoxycillin is in the range 1900 to 2600 mg, preferably 1950 to 2550 mg, and the amount of potassium clavulanate is such that the weight ratio of amoxycillin to clavulanate is from 1:14 to 1:20, at intervals of about 12 h.

Preferably, the dosage regimen provides a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.4 h, preferably at least 4.6 h, more preferably at least 4.8 h, most preferably for about 6 h or longer, and a mean maximum plasma concentration (C_{max}) of amoxycillin which is at least 12 μg/mL, preferably at least 14 μg/mL, more preferably at least 16 μg/mL.

More preferably, the dosage regimen provides a mean plasma concentration of amoxycillin of 8 μg/ml for at least 4.4 h, more preferably at least 4.6 h, most preferably at least 4.8 h.

In a further aspect, the present invention provides for a method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxycillin and potassium clavulanate such that the amount of amoxycillin is in the range 1400 to 1900 mg, preferably 1500 to 1900 mg, and the amount of potassium clavulanate is such that the weight ratio of amoxycillin to clavulanate is from 1:12 to 1:14, at intervals of about 12 h, such that the dosage regimen provides a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.4 h, preferably at least 4.6 h, more preferably at least 4.8h, and a mean maximum plasma concentration (C_{max}) of amoxycillin which is at least 12 μg/mL, preferably at least 14 μg/mL, more preferably at least 16 μg/mL.

Bacterial infections amenable to tablets of the present invention include infections caused by the organisms *S pneumoniae* (including Drug Resistant *S pneumoniae* (DRSP), for instance Penicillin Resistant *S pneumoniae* (PRSP)), and/or the β–lactamase producing respiratory pathogens, most notably *H influenzae* and *M catarrhalis*, such as respiratory tract infections, including community acquired pneumoniae (CAP), exacerbations of chronic bronchitis (AECB) and acute bacterial

sinusitis (ACB), where the higher break points achievable through the improved pharmacokinetic profile will be especially advantageous compared to existing antibacterial agents. Most outpatient respiratory infections are caused by either *S pneumoniae* and/or the β–lactamase producing bacteria and are treated empirically so there is a continuing need for a method of treatment, such as the present invention, that provides a spectrum of activity that covers all such pathogens. (D)PRSP are defined as *S pneumoniae* isolates with penicillin MICs ≥ 0.2 μg/mL.

The term "amoxycillin" is used generically to refer to both amoxycillin trihydrate and (crystalline) sodium amoxycillin, without distinction and unless otherwise indicated.

Unless otherwise indicated, weights of amoxycillin and clavulanate refer to the equivalent weights of the corresponding free acids. In addition, it will be appreciated that in practice, weights of amoxycillin and clavulanate to be incorporated into a formulation will be further adjusted, in accord with conventional practice, to take account of the potency of the amoxycillin and clavulanate.

In a first embodiment, a dosage of amoxycillin of from 1900 to 2600 mg and a corresponding amount of clavulanate may delivered from an immediate release formulation. Accordingly, in a further aspect, the present invention provides for method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxycillin and potassium clavulanate such that the amount of amoxycillin is in the range 1900 to 2600, preferably 1950 to 2550 mg, and the amount of potassium clavulanate is such that the weight ratio of amoxycillin to clavulanate is from 1:14 to 1:20, at intervals of about 12 h, wherein the dosage is delivered from an immediate formulation.

As used herein, the term "immediate release" refers to the release of the majority of the active material content within a relatively short time, for example within 1 hour, preferably within 30 minutes, after oral ingestion.

Representative dosages include 2000/125, 2250/125 and 2500/125 mg of amoxycillin and potassium clavulanate, respectively. A preferred dosage is 2000/125 mg of amoxycillin and potassium clavulanate.

The dosage in an immediate release formulation may be provided as a single tablet, for instance a chewable, optionally effervescent, tablet, a single dose capsule or a single dosage sachet, comprising, for instance, 2000, 2250 or 2500 mg amoxycillin and 125 mg potassium clavulanate. Alternatively, the dosage may be made up of a number of smaller tablets or capsules, for instance, 2, 3 or 4, some of which may be the same and some of which may comprise amoxycillin only and no potassium clavulanate. Thus, for instance, a dosage of 2000 mg amoxycillin and

125 mg potassium clavulanate may be provided by a combination of three tablets each comprising 500 mg amoxycillin and one tablet comprising 500 mg amoxycillin and 125 mg potassium clavulanate. Alternatively, such a dosage may be provided by two tablets each comprising 1000/62.5 mg amoxycillin/potassium clavulanate. In addition, a dosage of 2250 mg amoxycillin and 125 mg potassium clavulanate may be provided by a combination of four tablets comprising 500 mg amoxycillin and one tablet comprising 250 mg amoxycillin and 125 mg potassium clavulanate or two tablets comprising 875 mg amoxycillin and one tablet comprising 500 mg amoxycillin and 125 mg potassium clavulanate. Furthermore, a dosage of 2500 mg amoxycillin and 125 mg potassium clavulanate may be provided by a combination of four tablet comprising 500 mg amoxycillin and one tablet comprising 500 mg amoxycillin and 125 mg potassium clavulanate. Tablets comprising 500 and 875 mg amoxycillin and 250/125, 500/125 and 875/125 mg amoxycillin/potassium clavulanate are already commercially available.

It will be appreciated that immediate release tablets comprising 1000/62.5 mg are novel. Accordingly, in a further aspect, the present invention provides for an immediate release pharmaceutical tablet formulation comprising 1000 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanate, in a nominal ratio of about 16:1, in combination with pharmaceutically acceptable excipients or carriers. Immediate release tablets comprising 1000/62.5 mg can be readily prepared by adapting compositions previously described for 875/125 and 1000/125 mg tablets (see for instance, WO 95/28927 and WO 98/35672, SmithKline Beecham).

It will also be appreciated that immediate release single dosage sachets comprising 2000/125 mg, 2250/125 mg or 2500/125 mg, or the corresponding half quantities thereof, are novel. Accordingly, in a further aspect, the present invention provides for an immediate release pharmaceutical formulation in the form of a single dose sachet comprising 2000, 2250 or 2500 mg ±5% amoxycillin and 125 mg ±5% potassium clavulanate, in a nominal ratio of about 16:1, 18:1 or 20:1, respectively, or the corresponding half quantities thereof, in combination with pharmaceutically acceptable excipients or carriers. Such sachets can be readily prepared by adapting compositions previously described for 875/125 and 1000/125 mg sachets (see for instance, WO 92/19277 and WO 98/35672, SmithKline Beecham).

It will be further appreciated that immediate release chewable tablets comprising 2000, 2250 or 2500/125 mg are novel. Accordingly, in a further aspect, the present invention provides for an immediate release pharmaceutical formulation in the form of a chewable, optionally effervescent, tablet comprising 2000, 2250, or 2500 mg amoxycillin and 125 mg ±5% potassium clavulanate, in a nominal ratio of

about 16:1, 18:1 or 20:1, respectively, or the corresponding half quantities thereof, in combination with a chewable base and, if effervescent, an effervescent couple, and other pharmaceutically acceptable excipients or carriers. Such chewable tablets can be readily prepared by adapting compositions previously described for chewable tablets comprising amoxycillin and potassium clavulanate (see for instance, EP-A-0 396 335, Beecham Group and WO 98/35672, SmithKline Beecham).

In a second embodiment, a dosage of amoxycillin of from 1900 to 2600 mg and a corresponding amount of clavulanate may be delivered from a modified release formulation. Accordingly, in a further aspect, the present invention provides for method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxycillin and potassium clavulanate such that the amount of amoxycillin is in the range 1900 to 2600 mg, preferably 1950 to 2550 mg, and potassium clavulanate is present in pro rata amount such that the weight ratio of amoxycillin to clavulanate is from 1:14 to 1:20, at intervals of about 12 h, in which the dosage is delivered from a modified release formulation.

In a third embodiment, a dosage of amoxycillin of from 1400 to 1900 mg and a corresponding amount of clavulanate may be delivered from modified release formulation. Accordingly, in a further aspect, the present invention provides for method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxycillin and potassium clavulanate such that the amount of amoxycillin is in the range 1400 to 1900 mg, preferably 1500 to 1900 mg, and potassium clavulanate is present in pro rata amount such that the weight ratio of amoxycillin to clavulanate is from 1:12 to 1:14, at intervals of about 12 h, in which the dosage is delivered from a modified release formulation.

As used herein, the term "modified release" refers to a release of drug substance which is not immediate.

Representative dosages include 1500/125, 1750/125 and 2000/125 mg of amoxycillin and potassium clavulanate, respectively. A preferred dosage is 2000/125 mg of amoxycillin and potassium clavulanate.

The dosage in a modified release formulation may conveniently be provided as a number of tablets, for instance two, some of which may be the same and some of which may comprise amoxycillin only and no potassium clavulanate. Thus, for instance, a dosage of 2000 mg amoxycillin and 125 mg potassium clavulanate may be provided by two tablets each comprising 1000/62.5 mg amoxycillin/potassium clavulanate or one tablet comprising 1000 mg of amoxycillin and one tablet comprising 1000/125 mg amoxycillin/potassium clavulanate. In addition, a dosage of 1750 mg amoxycillin and 125 mg potassium clavulanate may be provided by two

tablets each comprising 875/62.5 mg amoxycillin/potassium clavulanate or one tablet comprising 875 mg of amoxycillin and one tablet comprising 875/125 mg amoxycillin/potassium clavulanate. A preferred tablet comprises 1000/62.5 mg amoxycillin/potassium clavulanate.

Preferably, in the modified release formulation, all the potassium clavulanate is provided in an immediate release phase whilst amoxycillin is provided in both an immediate release and a slow release phase.

Accordingly, in a further aspect, the present invention provides for a pharmaceutical formulation comprising amoxycillin and potassium clavulanate in which all of the potassium clavulanate and a first part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for immediate release of the potassium clavulanate and the first part of amoxycillin, to form an immediate release phase, and further comprising a second part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for slow release of the second part of amoxycillin, to form a slow release phase.

In a modified release formulation of the present invention, potassium clavulanate is released substantially immediately from the formulation, when the formulation reaches the stomach and is absorbed therefrom, thereby minimising the risk of degradation from prolonged exposure to the stomach. The amoxycillin release profile is made up of a contribution from the immediate release component. This is then complemented and extended by an on-going contribution from the slow release component.

As used herein, the term "slow release" refers to the gradual but continuous or sustained release over a relatively extended period of the active material content (in this case amoxycillin) after oral ingestion and which starts when the tablet reaches the stomach and starts to disintegrate/dissolve. The release will continue over a period of time and may continue through until and after the tablet reaches the intestine. This can be contrasted with the term "delayed release" in which release of the active does not start immediately the tablet reaches the stomach but is delayed for a period of time, for instance until when the tablet reaches the intestine when the increasing pH is used to trigger release of the active from the tablet.

Preferably, the modified release formulation has a biphasic profile with respect to amoxycillin, that is an initial burst from the immediate release phase to provide an acceptable C_{max} value, supplemented by a further contribution form the slow release phase, to extend the T>MIC parameter to an acceptable value.

Preferably, the modified formulation provides an "Area Under the Curve" (AUC) value which is substantially similar to, for instance at least 80%, preferably at

least 90%, more preferably about 100%, of that of the corresponding dosage of amoxycillin taken as a conventional (immediate release) formulation, over the same dosage period, thereby maximising the absorption of the amoxycillin component from the slow release component.

The pharmcokinetic profile for a unit dosage of the present invention may be readily determined from a single dosage bioavailability study in human volunteers. Plasma concentrations of amoxycillin may then be readily determined in blood samples taken from patients according to procedures well known and documented in the art.

Representative modified release formulations include a tablet, including a chewable, optionally effervescent tablet, a capsule, granules or a sachet, typically a tablet.

Representative modified release formulations having an immediate and a slow release phase provide a unit dosage in the range 700 to 1300 mg, preferably, 950 to 1300 mg, amoxycillin, for instance unit dosages of 1000, 875 and 750/62.5 mg amoxycillin/clavulanate. It will be appreciated that such 1000, 875 and 750/62.5 mg formulations are novel.

Accordingly, in a further aspect, the present invention provides for a pharmaceutical formulation having an immediate release phase and a slow release phase and comprising a unit dosage in the range 700 to 1300 mg, preferably, 950 to 1300 mg, amoxycillin, and a corresponding amount of potassium clavulanate, for instance unit dosages of 1000, 875 or 750 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanate, in a nominal ratio of about 16:1, 14;1 or 12;1, respectively, in combination with pharmaceutically acceptable excipients or carriers.

Preferably, the ratio of amoxycillin in the immediate and slow release phases is from 3:1 to 1:3, more preferably, from 3:2 to 2:3, yet more preferably 3:2 to 1:1. Representative ratios include about 2:1, 9:7 or 1:1. It is be found useful to employ an excess of amoxycillin in the immediate release phase, to ensure an adequate C_{max} value.

In the modified release formulations of the present invention, the portion of amoxycillin which is released immediately may be provided as amoxycillin trihydrate or (crystalline) sodium amoxycillin or a mixture thereof, preferably amoxycillin trihydrate, whilst the portion of amoxycillin which is released slowly is provided as amoxycillin trihydrate or (crystalline) sodium amoxycillin or a mixture thereof, preferably (crystalline) sodium amoxycillin.

Preferably, the modified release formulation is a tablet. In a preferred modified release tablet comprising 1000 mg amoxycillin and 62.5 mg potassium

clavulanate, the immediate release phase comprises about 563 mg ±5% amoxycillin and about 62.5 mg ±5% of potassium clavulanate and the slow release phase about 438 mg of amoxycillin, preferably crystalline sodium amoxycillin.

In a representative modified release tablet of the present invention, the immediate release phase comprises about 438 mg amoxycillin and about 62.5 mg of potassium clavulanate and the slow release phase about 438 mg of amoxycillin, preferably crystalline sodium amoxycillin, providing overall an 875/62.5 mg (14:1) tablet.

In a further representative tablet of the present invention, the immediate release phase comprises about 500 mg amoxycillin and about 62.5 mg of potassium clavulanate and the slow release phase about 250 mg of amoxycillin, preferably crystalline sodium amoxycillin, providing overall a 750/62.5 mg (12:1) tablet.

It will be appreciated that the use of a mixture of amoxycillin trihydrate and sodium amoxycillin is more generally applicable to other pharmaceutical formulations comprising amoxycillin and potassium clavulanate.

Accordingly, in a further aspect, the present invention provides for a pharmaceutical formulation comprising amoxycillin and potassium clavulanate in a ratio of from 1:1 to 30:1, preferably 2:1 to 20:1, more preferably 12:1 to 20:1, yet more preferably 14:1 to 16:1, in which amoxycillin is provided as a mixture of amoxycillin trihydrate and sodium amoxycillin in a ratio of from 3:1 to 1:3, more preferably from 3:2 to 2:3, yet more preferably 3:2 to 1:1. Preferably, sodium amoxycillin is crystalline sodium amoxycillin. Representative formulation types include tablets, including immediate release and modified release tablets as herein described, as well as other solid dosage forms such as capsules, single dosage sachets and granules. Representative tablet weights include 1000, 875, 500 and 250 mg amoxycillin and a corresponding weight of potassium clavulanate. Representative ratios include 4:1, 7:1, 8:1, 14; and 16:1. Preferably, in modified release formulations of the present invention, the amoxycillin in the immediate release phase consists essentially of amoxycillin trihydrate and the amoxycillin of the slow release phase consists essentially of sodium amoxycillin.

For a tablet formulation, the immediate and slow release phases may be provided in a number of different formats.

In a preferred aspect, the immediate and slow release phases are provided as separate layers of a layered tablet.

Accordingly, in a further aspect, the present invention provides for a layered tablet formulation comprising potassium clavulanate and amoxycillin in an immediate release layer phase and amoxycillin in a slow release layer. The layered

tablet may have two layers, or two layers plus one or more barrier layer, as well as a coating layer. As used herein, the term "bilayer" tablet refers to a tablet consisting of an immediate release and a slow release layer, optionally with a coating layer.

An immediate release layer may be, for example, a layer which disintegrates immediately or rapidly and has a composition similar to that of known tablets which disintegrates immediately or rapidly. For example, the layer may comprise, in addition to the active material content, excipients including diluents such as microcrystalline cellulose; disintegrants such as sodium starch glycollate, compression aids such as colloidal silicon dioxide and microcrystalline cellulose; and lubricants such as magnesium stearate. Such an immediate release layer may comprise around 60 to 85 % (all percentages given herein are on a weight percentage basis unless otherwise stated), preferably 70 to 85 %, of active material content, around 10 to 30 %, preferably 10 to 20 % of fillers/compression aids, and conventional amounts of disintegrants and lubricants, typically about 0.5 to 3%, etc.

An alternative type of immediate release layer may be a swellable layer having a composition which incorporates polymeric materials which swell immediately and extensively in contact with water or aqueous media, to form a water permeable but relatively large swollen mass. Active material content may be immediately leached out of this mass.

Slow release layers have a composition which comprises amoxycillin together with a release retarding excipient which allows for slow release of amoxycillin. Suitable release retarding excipients include pH sensitive polymers, for instance polymers based upon methacrylic acid copolymers such as the Eudragit (trade mark) polymers, for example Eudragit L (trade mark) which may be used either alone or with a plasticiser; release-retarding polymers which have a high degree of swelling in contact with water or aqueous media such as the stomach contents; polymeric materials which form a gel on contact with water or aqueous media; and polymeric materials which have both swelling and gelling characteristics in contact with water or aqueous media.

Release retarding polymers which have a high degree of swelling include, *inter alia*, cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethylamide, potassium methacrylatedivinylbenzene co-polymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone, high-molecular weight polyvinylalcohols etc.

Release retarding gellable polymers include methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, low-

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molecular weight polyvinylalcohols, polyoxyethyleneglycols, non-cross linked polyvinylpyrrolidone, xanthan gum etc.

Release retarding polymers simultaneously possessing swelling and gelling properties include medium-viscosity hydroxypropylmethylcellulose and medium-viscosity polyvinylalcohols.

A preferred release-retarding polymer is xanthan gum, in particular a fine mesh grade of xanthan gum, preferably pharmaceutical grade xanthan gum, 200 mesh, for instance the product Xantural 75 (also known as Keltrol CR, Trade Mark, Monsanto, 800 N Lindbergh Blvd, St Louis, MO 63167, USA). Xanthan gum is a polysaccharide which upon hydration forms a viscous gel layer around the tablet through which the active has to diffuse. It has been shown that the smaller the particle size, the slower the release rate. In addition, the rate of release of drug substance is dependent upon the amount of xanthan gum used and can be adjusted to give the desired profile.

Examples of other polymers which may be used include Methocel K4M (Trade Mark), Methocel E5 (Trade Mark), Methocel E5O (Trade Mark), Methocel E4M (Trade Mark), Methocel K15M (Trade Mark) and Methocel K100M (Trade Mark). An example of a suitable polymer mixture is a mixture of Methocel E5 and K4M, for example 1:1, w:w.

Other known release-retarding polymers which may be incorporated include hydrocolloids such as natural or synthetic gums, cellulose derivatives other than those listed above, proteinaceous substances such as acacia, gum tragacanth, locust bean gum, guar gum, agar, pectin, carageenin, soluble and insoluble alginates, carboxypolymethylene, gelatin, casein, zein, and the like.

Such a slow release layer may contain polymers which immediately swell in contact with water or aqueous media so that they form a relatively large swollen mass which is not immediately discharged from the stomach into the intestine.

The slow release layer may also include diluents such as microcrystalline cellulose; compression aids such as microcrystalline cellulose; and lubricants such as magnesium stearate. The slow release layer may further comprise disintegrants, such as sodium starch glycollate; binders such as povidon (polyvinylpyrrolidone); desiccants, such as silicon dioxide; and soluble excipients such as mannitol or other soluble sugars. Typically, the slow release layer comprises from about 60 to 80% by weight of amoxycillin; from 10 to 20 % by weight of diluent/compression aid and from 1 to 2.5 % by weight of lubricant.

When xanthan gum is used as release-retarding polymer, the layer contains from 60 to 80% of amoxycillin, from 1 to 25%, preferably 2 to 15%, more preferably

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4 to 15% of xanthan gum, from 10 to 30%, preferably 10 to 20% of fillers/compression aids, and conventional quantities of lubricants, all % being by weight of the layer. In a preferred embodiment, the slow release layer comprises from 70 to 80% of amoxycillin, from 4 to 10%, of xanthan gum, from 10 to 20% of microcrystalline cellulose, and from 1 to 2 5 % of magnesium stearate, all % being by weight of the layer.

When release-retarding polymers other than xanthan gum are used, the slow release layer may contain around 30 to 70%, preferably from 40 to 60%, of amoxycillin, from 15 to 45% of release-retarding polymer, from 0 to30% of fillers/compression aids, conventional quantities of lubricants, and from 5 to 20% of soluble excipients, all % being by weight of the layer.

It has also been surprisingly found that when the amoxycillin in the slow release layer is in the form of a soluble salt thereof, such as sodium amoxycillin, then the release thereof may be retarded by the inclusion of an organic acid.

Accordingly, in a further aspect, the present invention provides for the use of a pharmaceutically acceptable organic acid as a release retarding excipient in a formulation comprising a pharmaceutically acceptable soluble salt of amoxycillin, for instance sodium amoxycillin.

It will be appreciated that the use of an organic acid as a release retarding excipient is more generally applicable beyond the particular formulations hereinbefore described.

Accordingly, the present invention further provides for a pharmaceutical formulation comprising a pharmaceutically acceptable soluble salt of amoxycillin, for instance sodium amoxycillin, in a slow release phase which further comprises a release retarding excipient which is a pharmaceutically acceptable organic acid present in a molar ratio of from 100:1 to 1:10, preferably 50:1 to 1:5, more preferably 20:1 to 1:2 (amoxycillin salt to organic acid).

Soluble pharmaceutically acceptable salts of amoxycillin include alkali metal salts such as sodium and potassium; alkaline earth metal salts such as magnesium and calcium, and acid salts such as amoxycillin hydrochloride or sulphate. Preferably, the salt is sodium amoxycillin, preferably crystalline sodium amoxycillin.

Pharmaceutically acceptable organic acid for use in the present invention are preferably solid and include mono-carboxylic acids and poly-carboxylic acids having from 2 to 25, preferably from 2 to 10, carbon atoms; monocyclic and polycyclic aryl acids such as benzoic acid; as well as monohydrogen, dihydrogen etc metal salts of multi-valent acids. A single pharmaceutically acceptable organic acid may be used, or two or more of such may be used in combination. Preferably, the organic acid is a

$C_{(2-10)}$alkyl- or alkenyl- carboxylic acid having from one to or three carboxylic acid groups, and optionally with one or more hydroxy substituents or an additional CO group in the carbon chain, for instance malonic acid, succinic acid, fumaric acid, maleic acid, adipic acid, lactic acid, levulinic acid, sorbic acid or a fruit acid such as tartaric acid, malic acid, ascorbic acid or citric acid, or an acidic salt thereof, more preferably citric acid.

The organic acid may be used alone or in combination with a release retarding polymer as hereinbefore described. A preferred combination comprises citric acid and a release retarding gellable polymer, in particular xanthan gum. In the presence of the organic acid, for instance citric acid, xanthan gum may be used at a lower level then when included on its own, for instance, from 0.5 to 8%, preferably 1 to 5%, typically about 2%, by weight of the slow release layer.

When an organic acid is used as release-retarding polymer, the slow release layer contains from 60 to 80% of amoxycillin, from 10 to 30%, preferably 10 to 20% of fillers/compression aids, and conventional quantities of lubricants, all % being by weight of the layer. In a preferred embodiment, the slow release layer comprises from 60 to 70 % of amoxycillin, from 10 to 20% of microcrystalline cellulose, and from 1 to 2 5 % of magnesium stearate, all % being by weight of the layer.

In a representative example, a layered tablet comprises in the slow release layer crystalline sodium amoxycillin and citric acid, in a molar ratio of about 50:1 to 1:2, preferably 20:1 to 1:2, more preferably 2:1 to 1:1.2, yet more preferably about 1:1. In a preferred embodiment, the slow release layer comprises about 438 mg ±5% crystalline sodium amoxycillin, about 78 mg ±10% citric acid and about 2% by weight of xanthan gum.

In a preferred layered tablet comprising 1000 mg amoxycillin and 62.5 mg potassium clavulanate, the immediate release layer comprises about 563 mg ±5% amoxycillin and about 62.5 mg ±5% of potassium clavulanate and the slow release layer about 438 mg ±5% of amoxycillin, preferably crystalline sodium amoxycillin, about 78 mg ±10% citric acid and about 2% by weight of xanthan gum.

The tablet formulations of the invention may also include one or more barrier layers, which may be located between the respective first and second layers, and/or on one or more of the outer surfaces of the first and second layers, for example the end faces of the layers of a substantially cylindrical tablet. Such barrier layers may, for example, be composed of polymers which are either substantially or completely impermeable to water or aqueous media, or are slowly erodable in water or aqueous media or biological liquids and/or which swell in contact with water or aqueous media. Suitably the barrier layer should be such that it retains these characteristics at

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least until complete or substantially complete transfer of the active material content to the surrounding medium.

Suitable polymers for the barrier layer include acrylates, methacrylates, copolymers of acrylic acid, celluloses and derivatives thereof such as ethylcelluloses, cellulose acetate propionate, polyethylenes and polyvinyl alcohols etc. Barrier layers comprising polymers which swell in contact with water or aqueous media may swell to such an extent that the swollen layer forms a relatively large swollen mass, the size of which delays its immediate discharge from the stomach into the intestine. The barrier layer may itself contain active material content, for example the barrier layer may be a slow or delayed release layer. Barrier layers may typically have an individual thickness of 2 mm to 10 microns.

Suitable polymers for barrier layers which are relatively impermeable to water include the Methocel (trade mark) series of polymers mentioned above, for example Methocel K100M, Methocel K15M, Methocel E5 and Methocel E50, used singly or combined, or optionally combined with an Ethocel (trade mark) polymer. Such polymers may suitably be used in combination with a plasticiser such as hydrogenated castor oil. The barrier layer may also include conventional binders, fillers, lubricants and compression acids etc such as Polyvidon K30 (trade mark), magnesium stearate, and silicon dioxide, e.g. Syloid 244 (trade mark).

The tablet formulation of the invention may be wholly or partly covered by a coating layer, which may be a protective layer to prevent ingress of moisture, or damage to the tablet. The coating layer may itself contain active material content, and may, for example, be an immediate release layer, which immediately disintegrates in contact with water or aqueous media to release its active material content, for example amoxycillin and potassium clavulanate. Preferred coating materials comprise hydroxypropylmethylcellulose and polyethylene glycol, with titanium dioxide as an opacifying agent, for instance as described in WO 95/28927 (SmithKline Beecham).

As well as active material content etc, the tablet of the invention may also include a pH modifying agent, such as a pH buffer, which may be contained in either the immediate-, or slow-release layers, or in a coating around all or part of the tablet. A suitable buffer is calcium hydrogen phosphate.

In a tablet without a barrier layer, the immediate release layer comprises form 50 to 60% and the slow release layer comprises from 40 to 50% of the overall tablet weight. When a barrier layer is present, the immediate release layer typically comprises from 40 to 50%, the slow release layer comprises from 35 to 45%, and the barrier layer comprises from 5 to 20% of the overall tablet weight.

It is found that a satisfactory pharmacokinetic profile may be obtained from a bilayered tablet of the present invention without the need to include a barrier layer. Accordingly, a bi-layer tablet is preferred. This also reduces the complexity of the manufacturing process.

It will be appreciated that 1000, 875 and 750/62.5 mg bi-layer tablets having an immediate release layer and a slow release layer are novel. Accordingly, in a further aspect, the present invention provides for a pharmaceutical bi-layer tablet formulation having an immediate release phase and a slow release phase and comprising from 700 to 1250 mg amoxycillin and a pro rata amount of potassium clavulanate, preferably 1000, 875 or 750 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanate, in a nominal ratio of about 16:1, 14;1 or 12;1, respectively, in combination with pharmaceutically acceptable excipients or carriers.

Suitably the tablet formulations of the invention may be formed by known compression tabletting techniques for example using a known multi-layer tabletting press. Preferably, in a preliminary step, slugging or roller compaction is used to form granulates. Lubricants and compression aids (if used) are then added, to form a compression blend for subsequent compaction. Alternatively, a dry densification process may be used, e.g. briquetting. Typically the active material content, pH modifiers, buffers, fillers and/or diluent, release retarding agents, disintegrants and binders, when used are mixed, then lubricants and compression aids are added. The complete mixture may then be compressed under high pressure in the tablet press. A wet granulation process may be also be used, for instance with isopropanol as the solvent and Polyvidon K-30 (trade mark) as the wet granulating aid.

A barrier layer, if present, may typically be made up by a wet granulation technique, or by dry granulation techniques such as roller compaction. Typically the barrier material, e.g. Methocel (trade mark) is suspended in a solvent such as ethanol containing a granulation acid such as Ethocel or Polyvidon K-30 (trade mark), followed by mixing, sieving and granulation. Typically a first layer may be formed, then a barrier layer deposited upon it, e.g. by compression, spraying or immersion techniques, then the second layer may be formed so that the barrier layer is sandwiched between the first and second layers. Additionally, or alternatively, the first and second layers may be formed and a barrier layer may then be formed, for instance by compression, spraying or immersion, on one or more of the end faces of the tablet.

Potassium clavulanate is known to be extremely water sensitive. Therefore tablet formulations which contain potassium clavulanate should be made up in dry conditions, preferably at 30% relative humidity or less, and the ingredients of the

formulation should be pre-dried where appropriate. Tablet formulations of the invention should be stored in containers which are sealed against the ingress of atmospheric moisture.

Tablet cores may then be coated with a coating layer which may be applied form an aqueous or an organic solvent system, preferably an aqueous solvent system, to provide film coated tablets.

The invention also provides a method for the manufacture of a tablet formulation as described above comprising the steps of forming said first and second layers, and any barrier layers and coating layer(s) which may be present.

In addition to the layered tablet approach hereinbefore described, other types of tablet may be used to provide an immediate release phase and a slow release phase, using the excipients hereinbefore described but providing the phases in different formats. Thus, the slow release phase may form the core of a tablet which is then surrounded by an outer casing forming the immediate release phase, optionally with an intermediate coating layer around the core and/or a final coating layer around the outer casing (see WO 95/28148, SmithKline Beecham). The slow release phase may also be provided as granules which are dispersed in a matrix of amoxycillin and potassium clavulanate, the matrix forming the immediate release phase (see WO 96/04908, SmithKline Beecham). In a further variant, a tablet may be prepared from slow release granules comprising amoxycillin and immediate release granules comprising amoxycillin and potassium clavulanate (as described in WO 92/19227, SmithKline Beecham) or immediate release granules comprising amoxycillin and potassium clavulanate, for instance in a 2:1 ratio, and further immediate release granules comprising amoxycillin (as described in WO 98/35672, SmithKline Beecham Laboratoires Pharmaceutiques), the granules being combined with extragranular excipients to form tablets. Such granules may also be processed into other pharmaceutical formulations, for instance single dosage sachets, capsules or chewable tablets.

In a further embodiment, the slow release phase may be provided as a separate tablet, so that the unit dosage is provided as a combination of a conventional tablet in which amoxycillin and potassium clavulanate are released immediately, optionally with a conventional amoxycillin tablet, and a tablet comprising amoxycillin (and no potassium clavulanate) from which amoxycillin is released slowly. The weight of potassium clavulanate and the combined weights of amoxycillin in the conventional and slow release tablets will provide the overall unit dosage. Thus, for instance a dosage of 2000/125 mg may be provided by a combination of an existing 500/125 mg amoxycillin/potassium clavulanate tablet

and a 500 mg amoxycillin tablet in combination with a slow release tablet comprising 1000 mg of amoxycillin. Furthermore, a dosage of 1750/125 mg may be provided by an existing 875/125mg tablet (as described in WO 95/28927, SmithKline Beecham) in combination with a slow release tablet comprising 875 mg of amoxycillin. In addition, a dosage of 1500/125 mg may be provided by an existing 500/125mg tablet and an existing 500 mg tablet of amoxycillin in combination with a slow release tablet comprising 500 mg of amoxycillin. Accordingly, in a further aspect, the present invention provides for a kit comprising a conventional (immediate release) tablet comprising amoxycillin and potassium clavulanate, optionally with a conventional (immediate release) tablet comprising amoxycillin, and a slow release tablet comprising amoxycillin (and no potassium clavulanate).

In a further aspect, the present invention provides for a pharmaceutical tablet comprising amoxycillin (as the sole active ingredient) formulated with a release retarding excipient which causes a slow release of the amoxycillin from the tablet, and excluding tablets which comprise from 400 to 500mg amoxycillin trihydrate or a mixture comprising at least 70% amoxycillin trihydrate and up to 30% sodium amoxycillin and hydroxypropyl methylcellulose.

Such tablets may comprise from 100 to 1250mg amoxycillin which may be amoxycillin trihydrate or (crystalline) sodium amoxycillin or a mixture thereof, for instance 500, 875 or 1000mg amoxycillin. Suitable excipients for slow release are those hereinbefore described for slow release layers. The tablet may comprise from 1 to 25%, preferably from 2 to 15%, more preferably 4 to 10% of xanthan gum, or from 10 to 25, preferably 15 to 20% of a hydroxypropylmethylcellulose, for instance Methocel K100LV or Methocel K4M. Alternatively, such tablets may comprise citric acid, optionally with xanthan gum, as hereinbefore described.

The invention will now be described by way of example only with reference to the accompanying drawings, in which:

Fig. 1 shows the structure of various types of layered tablets of the present invention, in particular the structure of substantially cylindrical compressed tablets are shown in longitudinal section. In Fig 1A, the tablet comprises a first layer (1) and a second layer (2), without any barrier layer or coating layer. In Fig 1B, the tablet comprises a first layer (1), a second layer (2), and a barrier layer (3) sandwiched between the first and second layers (1) and (2). In Fig 1C, the tablet comprises a first layer (1), a second layer (2), and a barrier layer (3) located on the end face of the second layer (2). In Fig 1D, the tablet comprises a first layer (1), a second layer (2), a barrier layer (3) sandwiched between the first and second layers

(1) and (2), and a coating layer (4) which partly covers the tablet. The dotted line shows the possibility of the coating layer (4A) covering the entire tablet. In Fig. 1E, the tablet comprises a first layer (1) a second layer (2), and a third layer (3) intermediate between the first and second layers (1) and (2). All three of these layers (1), (2) and (3) include active material content.

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also incorporated by reference herein in its entirety in the manner described above for publications and references.

Example 1 – 1000/62.5 mg modified release tablet

Name of Ingredient	mg/tablet	% w/w
Immediate Release Layer		
Amoxycillin Trihydrate	654.1*	40.88
Clavulanate Potassium	76.2#	4.76
Microcrystalline Cellulose	136.4	8.52
Sodium Starch Glycollate	18.0	1.12
Colloidal Silicon Dioxide	6.3	0.39
Magnesium Stearate	9.0	0.56
Total (Immediate Release Layer)	**900.0**	**56.23**
Slow Release Layer		
Sodium Amoxycillin	480.8**	30.05
Microcrystalline Cellulose	113.2	7.08
Xanthan Gum	14.0	0.87
Citric Acid	78.0	4.87
Magnesium Stearate	14.0	0.87
Total (Sustained Release Layer)	**700.0**	**43.74**
Film coat – Opadry YS-1-7700 Composition		
Hydroxypropylmethylcellulose 2910 6cp	11.6	
Hydroxypropylmethylcellulose 2910 15cp	3.9	
Titanium dioxide	15.1	
Polyethylene Glycol 3350	2.3	
Polyethylene Glycol 8000	2.3	
Total weight of coated tablet	1635.2	

* Equivalent to 562.5 mg of amoxycillin based on an assay of 86.0%
Equivalent to 62.5 mg of clavulanic acid based on an assay of 82.0%
**Equivalent to 437.5 mg amoxycillin based on an assay of 91.0%

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X
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Example 2 – 1000/62.5 mg modified release tablet The immediate release layer and film coat are as for the tablet of Example 1

Name of Ingredient	mg/tablet	% w/w
Slow Release Layer		
Sodium Amoxycillin	480.8**	30.05
Microcrystalline Cellulose	127.2	7.95
Citric Acid	78.0	4.87
Magnesium Stearate	14.0	0.87
Total (Slow Release Layer)	**700.0**	**43.74**
Total Weight of coated tablet	**1635.2**	

**Equivalent to 437.5 mg amoxycillin based on an assay of 91.0%

Preparation of modified release tablets

Amoxycillin trihydrate, potassium clavulanate, microcrystalline cellulose and sodium starch glycollate were blended, compacted and milled to form granules. Magnesium stearate and colloidal silicon dioxide were then added to these granules and blended to form the immediate release compression blend.

Sodium amoxycillin, microcrystalline cellulose, citric acid and xanthan gum (if applicable) were blended, compacted and milled to form granules. Magnesium stearate was added to these granules and blended to form the slow release compression blend.

The two blends were then compressed as separate layers on a bilayer tablet press to form bilayer tablets. Finally, the tablets were coated in an aqueous film coating process in a perforated pan.

Example 3 - Slow release tablet (875 mg)

(a) Sodium Amoxycillin Tablet

	mg/tablet	%
Sodium Amoxycillin 91%*	961.54	73.96
Dried Microcrystalline Cellulose	273.46	21.04
Magnesium Stearate	13.0	1.00
Xanthan gum 200 mesh**	52.0	4.00
Total	1300	100

(b) Sodium Amoxycillin Tablet with citric acid

	mg/tablet	%
Sodium Amoxycillin 91%*	961.54	66.31
Dried Microcrystalline Cellulose	288.96	19.92
Magnesium Stearate	14.50	1.00
Citric acid	156	10.75
Xanthan gum 200 mesh**	29.0	2.00
Total	1450	100

(c) **Amoxycillin Trihydrate Tablet**

	mg/tablet	%
Amoxycillin Trihydrate 86%*	1017.4	78.26
Dried Microcrystalline Cellulose	217.6	16.74
Magnesium Stearate	13.0	1.00
Xanthan Gum, 200 mesh**	52.0	4.00
Total	1300	100

* adjusted for the potency of the amoxycillin component and corresponding to 875 mg amoxycillin,

** Xantural 75

Example 4 – 875/62.5 mg modified release tablet

Slow release layer

This may be formed using half the quantities given above, for a slow release layer comprising about 438 mg amoxycillin.

Immediate release layer – 1

Amoxycillin trihydrate	507 mg
(equiv to amoxycillin free acid)	(438)
Potassium clavulanate	71.8
(equivalent to clavulanic acid)	(62.5)
Microcrystalline cellulose (Avicel PH102)	125
Sodium starch glycollate (Explotab)	26
Magnesium stearate	6.5

The immediate release layer comprises nominally 438/62.5mg amoxycillin/clavulanate.

Immediate release layer - 2

Amoxycillin trihydrate	507mg
(equiv to amoxycillin free acid)	(438)
Potassium clavulanate	71.8
(equivalent to clavulanic acid)	(62.5)
Microcrystalline cellulose (Avicel PH102)	135
Sodium starch glycollate (Explotab)	34
Talc	67
Magnesium stearate	25
Silica (Syloid)	17

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The immediate release layer comprises nominally 438/62.5mg amoxycillin/clavulanate.

Barrier Layers

Barrier layers and methods for their preparation are described in WO 95/20946 (SmithKline Beecham).

Preparation of Tablets

The active ingredients, fillers and diluents (microcrystalline cellulose), release controlling agents (if present), disintegrants (crospovidone, sodium starch glycollate) etc are mixed. Lubricants (talc, Mg-stearate) and colloidal silicon dioxide (Syloid 244) are added, and mixing is continued for another minute. The complete mixture is slugged on a tablet press or roller compacted (briquetting step), followed by size reduction (Apex, Fitzmill, Frewitt) and passage through an oscillatory sieve or particle size classifier (Kason, Sweco). If the flow properties are unsatisfactory, the briquetting step is repeated. Separate compressed blends are prepared for the immediate and slow release layers, and barrier layer, if present.

In some cases, where the bulk density is rather low, a densifying step (pre-tabletting and sieving as in the briquetting method) may be required in order to achieve the nominal weight of a particular layer.

The blends are then compressed as separate layers on a layer tablet press to form bilayered tablets. Tablets may then be coated with a white opaque coating, for instance the product Opadry, Opaspray (Colorcon).

Example 5 - Dissolution Testing Methods

The release of amoxycillin and clavulanate from tablets into static media may be measured using the USP Dissolution Test Method II.

Test specifications:

Temperature:	37.0 ± 0.5°C
Test medium:	Deionized water

Method

The drug release periodically up to 8 h is determined.

in vivo **Pharmacokinetic evaluation of formulations**

The bioavailability of formulations according to the present invention were evaluated in a human volunteer study.

Each formulation was administered with food and blood samples were taken 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h after dosing.

Study A

The first study compared:

a dosage of 1750/125 mg amoxycillin/potassium clavulanate, made up of a combination of one modified release tablet comprising 875/125 mg amoxycillin trihydrate/clavulanate and 4% xanthan gum and one immediate release tablet comprising 875 mg amoxycillin trihydrate (formulation I);

a dosage of 1750/125 mg amoxycillin/potassium clavulanate, made up of a combination of one modified release tablet comprising 875/125 mg crystalline sodium amoxycillin/clavulanate and 4% xanthan gum and one immediate release tablet comprising 875 mg amoxycillin trihydrate (formulation II);

a dosage of 1750/125 mg amoxycillin/potassium clavulanate, made up of a combination of one modified release tablet comprising 875/125 mg crystalline sodium amoxycillin/clavulanate, citric acid (156 mg) and 2% xanthan gum and one immediate release tablet comprising 875 mg amoxycillin trihydrate (formulation III);

a dosage of 1500/125 mg amoxycillin/potassium clavulanate (made up of a modified release tablet comprising 500/125 mg crystalline sodium amoxycillin/potassium clavulanate and two immediate release tablet comprising 500 mg amoxycillin trihydrate (Amoxyl, SmithKline Beecham) (formulation IV); and

a dosage of 1750/125 mg amoxycillin/potassium clavulanate, made up of a combination of one immediate release tablet comprising 875/125 mg amoxycillin trihydrate/clavulanate (Augmentin, SmithKline Beecham) and one immediate release tablet comprising 875 mg amoxycillin trihydrate (Amoxyl, SmithKline Beecham) (formulation V).

Results

Formulation	n	Cmax[1]	T>MIC[1,2]	AUC[1,3]
I	8	12.75 (4.96)	4.5 (1.8)	47.83
II	8	18.56 (4.72)	4.4 (1.0)	57.46
III	8	13.03 (2.34)	5.73 (2.54)	54.93
IV	8	17.33 (4.66)	4.8 (0.9)	56.71
V	40	20.21 (6.09)	4.2 (0.9)	56.33

() standard deviation

1 arithmetic mean value

2 T>MIC is the time above an amoxycillin concentration of 4 µg/ml

3 Area under the curve

The pharmacokinetic profile is shown in Figure 2.

Study B

The second study investigated:

a dosage of 2000/125 mg amoxycillin/potassium clavulanate, made up of two bilayer tablets according to Example 1 (formulation VI);

a dosage of 2000/125 mg amoxycillin/potassium clavulanate, made up of two bilayer tablets according to Example 2 (formulation VII);

a dosage of 2000/125 mg amoxycillin/potassium clavulanate, made up of a combination of three tablets each comprising 500 mg amoxycillin (Amoxyl, SmithKline Beecham) and one tablet comprising 500 mg amoxycillin and 125 mg potassium clavulanate (Augmentin, SmithKline Beecham) (formulation VIII).

Results

Formulation	N	Cmax[1]	T>MIC[1,2]	T>MIC[1,3]	AUC[1,4]
VI	8	17.41 (1.93)	6.0 (1.3)	4.8 (1.2)	74.9
VII	8	17.46 (6.02)	5.9 (1.3)	4.0 (1.3)	71.5
VIII	40	23.75 (5.73)	4.9 (1.1)	3.5 (1.0)	69.2

() standard deviation

1 arithmetic mean value

2 T>MIC is the time above an amoxycillin concentration of 4 μg/ml

3 T>MIC is the time above an amoxycillin concentration of 8 μg/ml

4 Area under the curve

Comparison of the AUC values for formulations VI and VII (bilayer tablets) against VII (immediate release tablets) shows that the absorption of the amoxycillin component has not been compromised by formulating a part of it in a slow release layer. This means that there is no extra, unabsorbed amoxycillin which may otherwise cause problems further down in the GI tract.

It was also found that for formulation VI, there was less inter-subject variability in the amoxycillin plasma concentrations than for formulation VII. This was otherwise the same, except that formulation VI also comprised xanthan gum (2%) in the slow release layer.

The pharmacokinetic profile for amoxycillin plasma concentration is shown in Figure 3 (in which A is formulation V, B is formulation VI, D is formulation VIII).

The pharmacokinetic profile for the clavulanate component was substantially the same for the bilayer tablets and the immediate release tablets, showing that the bioavailability thereof was not compromised by incorporation into the immediate release layer of a bilayer tablet.

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Reference Data

The existing Augmentin 875/125mg tablet has a C_{max} value of 11.6±2.8 µg/ml (Physicians Desk Reference, Medical Economics Co, 52 edition, 1998, 2802). The time above MIC was about 40% of the 12 hour dosing interval for an MIC of 2 µg/ml and about 30% for an MIC of 4 µg/ml (SmithKline Beecham data).

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Claims

1. A method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxycillin and potassium clavulanate such that the amount of amoxycillin is in the range 1900 to 2600 mg and the amount of potassium clavulanate is such that the weight ratio of amoxycillin to clavulanate is from 1:14 to 1:20, at intervals of about 12 hours.

2. A method as claimed in claim 1 in which the dosage regimen provides a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.4 h and a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 12 μg/mL.

3. A method as claimed in claim 2 in which the dosage regimen provides a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.8 h and a mean maximum plasma concentration (C_{max}) of amoxycillin of at least 16 μg/mL.

4. A method as claimed in claim 1 in which the dosage regimen provides a mean plasma concentration of amoxycillin of 8 μg/mL for at least 4.4 h.

5. A method as claimed in claim 1 in which the dosage is delivered from an immediate release formulation.

6. A method as claimed in claim 5 in which the dosage is 2000/125, 2250/125 or 2500/125 mg of amoxycillin and potassium clavulanate, respectively.

7. A method as claimed in claim 6 in which the dosage is provided as a single tablet, or as a number of smaller tablets, some of which may be the same and some of which may comprise amoxycillin only and no potassium clavulanate.

8. A method as claimed in claim 1 in which the dosage is delivered from a modified release formulation.

9. A method as claimed in claim 8 in which the dosage is provided as a number of tablets, some of which may be the same and some of which may comprise amoxycillin only and no potassium clavulanate.

10. A method as claimed in claim 8 in which the dosage is 2000/125 mg of amoxycillin and potassium clavulanate.

11. A method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxycillin and potassium clavulanate such that the amount of amoxycillin is in the range 1400 to 1900 mg, preferably 1500 to 1900 mg, and an amount of potassium clavulanate such that the weight ratio of amoxycillin to clavulanate is from 1:12 to 1:14, at intervals of about 12 h, such that the dosage regimen provides a mean plasma concentration of amoxycillin of 4 μg/mL for at least 4.4 h, and a mean maximum plasma concentration (Cmax) of amoxycillin of at least 12 μg/mL.

12. A method as claimed in claim 11 in which the dosage regimen provides a mean plasma concentration of amoxycillin of 4 μg/ml for at least 4.8 h and a mean maximum plasma concentration (Cmax) of amoxycillin of at least 16 μg/ml.

13. A method as claimed in claim 11 in which the dosage is delivered from a modified release formulation.

14. A method as claimed in claim 13 in which the dosage is 1500/125 or 1750/125 mg of amoxycillin and potassium clavulanate.

15. A method as claimed in claim 1 in which the infection is caused by the organisms *S pneumoniae* (including Drug Resistant and Penicillin Resistant *S pneumoniae*), *H influenzae* and/or *M catarrhalis*.

16. An immediate release pharmaceutical tablet formulation comprising 1000 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanate, in a nominal ratio of about 16:1, in combination with pharmaceutically acceptable excipients or carriers.

17. An immediate release pharmaceutical formulation in the form of a single dose sachet comprising 2000, 2250 or 2500 mg ±5% amoxycillin and 125 mg ±5% potassium clavulanate, in a nominal ratio of about 16:1, 18:1 or 20:1, respectively, or the corresponding half quantities thereof, in combination with pharmaceutically acceptable excipients or carriers.

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18. An immediate release chewable, optionally effervescent, tablet comprising 2000, 2250, or 2500 mg amoxycillin and 125 mg ±5% potassium clavulanate, in a nominal ratio of about 16:1, 18:1 or 20:1, respectively, or the corresponding half quantities thereof, in combination with a chewable base and, if effervescent, an effervescent couple, and other pharmaceutically acceptable excipients or carriers.

19. A modified release pharmaceutical formulation comprising amoxycillin and potassium clavulanate in which all of the potassium clavulanate and a first part of amoxycillin are formulated with pharmaceutically acceptable excipients which allow for immediate release of the potassium clavulanate and the first part of amoxycillin, to form an immediate release phase, and further comprising a second part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for slow release of the second part of amoxycillin, to form a slow release phase.

20. A modified release formulation as claimed in claim 19 which has a biphasic profile with respect to amoxycillin.

21. A modified release formulation as claimed in claim 19 which has an AUC value which is at least 80% of that of the corresponding dosage of amoxycillin taken as a conventional (immediate release) tablet(s), over the same dosage period.

22. A pharmaceutical formulation as claimed in claim 19 in which the ratio of amoxycillin in the immediate and slow release phases is from 3:1 to 1:3.

23. A pharmaceutical formulation as claimed in claim 19 comprising a unit dosage in the range 700 to 1300 mg, preferably, 950 to 1300 mg, amoxycillin and a corresponding amount of potassium clavulanate.

24. A pharmaceutical formulation as claimed in claim 23 in which the unit dosage is 1000, 875 or 750 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanate, in a nominal ratio of about 16:1, 14;1 or 12;1, respectively, in combination with pharmaceutically acceptable excipients or carriers.

25. A pharmaceutical formulation as claimed in claim 24 which is a tablet formulation.

26. A pharmaceutical tablet as claimed in claim 25 comprising 1000 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanate, in a nominal ratio of about 16:1 in which the immediate release phase comprises about 563 mg ±5% amoxycillin and about 62.5 mg ±5% of potassium clavulanate and the slow release phase comprises about 438 mg ±5% of amoxycillin.

27. A pharmaceutical formulation as claimed in claim 19 in which the amoxycillin of the slow release phase consists essentially of crystalline sodium amoxycillin.

28. A pharmaceutical formulation as claimed in claim 19 which is a layered tablet and in which the immediate and slow release phases are provided as separate layers of a layered tablet.

29. A tablet formulation as claimed in claim 28 in which the slow release layer comprises a release retarding excipient which is selected from a pH sensitive polymers; a release-retarding polymer which has a high degree of swelling in contact with water or aqueous media; a polymeric material which form a gel on contact with water or aqueous media; and a polymeric material which have both swelling and gelling characteristics in contact with water or aqueous media.

30. A tablet formulation as claimed in claim 29 in which the release retarding gellable polymer is selected from methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, low-molecular weight polyvinylalcohols, polyoxyethyleneglycols, and non-cross linked polyvinylpyrrolidone, or xanthan gum.

31. A tablet formulation as claimed in claim 29 in which the release retarding excipient is xanthan gum.

32. A tablet formulation as claimed in claim 31 in which the xanthan gum is present in from 1 to 25% by weight of the layer.

33. A tablet formulation as claimed in claim 28 in which the slow release layer comprises from 70 to 80% of amoxycillin, from 1 to 25% of xanthan gum, from 10 to 20% of fillers/compression aids, and conventional quantities of lubricants.

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34. A tablet formulation as claimed in claim 28 in which the slow release phase comprises sodium amoxycillin and in which the release retarding excipient is a pharmaceutically acceptable organic acid present in a molar ratio of from 100:1 to 1:10 (amoxycillin salt to organic acid).

35. A tablet formulation as claimed in claim 34 in which the pharmaceutically acceptable acid is citric acid present in a molar ratio of about 50:1 to 1:2.

36. A tablet formulation as claimed in claim 35 further comprising a release retarding gellable polymer.

37. A tablet formulation as claimed in claim 36 in which the release retarding gellable polymer is xanthan gum.

38. A tablet formulation as claimed in claim 36 in which xanthan gum is present in from 0.5 to 8% by weight of the slow release layer.

39. A tablet formulation as claimed in claim 34 which comprises 1000 mg ±5% of amoxycillin and 62.5 mg ±5% of potassium clavulanate and which comprises in the slow release layer about 438 mg ±5% of crystalline sodium amoxycillin, about 78 mg ±10% of citric acid and about 2% by weight of xanthan gum

40. A pharmaceutical formulation as claimed in claim 19 formed from slow release granules comprising amoxycillin and immediate release granules comprising amoxycillin and potassium clavulanate or immediate release granules comprising amoxycillin and potassium clavulanate and further immediate release granules comprising amoxycillin.

41. A method of treating bacterial infections in humans which comprises administering thereto a dosage of amoxycillin and potassium clavulanate which comprises nominally about 2000 mg ±5% of amoxycillin and nominally about 125 mg ±5% of potassium clavulanate, twice daily.

42. A pharmaceutical formulation comprising 1000mg ±5% amoxycillin and 62.5mg ±5% potassium clavulanic acid, in a nominal ratio of about 16:1, in combination with pharmaceutically acceptable excipients or carriers.

43. A formulation as claimed in claim 42 in which the amoxycillin is present as a mixture of amoxycillin trihydrate and sodium amoxycillin in a ratio of 3:1 to 1:3.

44. A pharmaceutical formulation comprising amoxycillin and potassium clavulanate in a ratio of from 1:1 to 30:1 in which amoxycillin is provided as a mixture of amoxycillin trihydrate and sodium amoxycillin in a ratio of from 3:1 to 1:3.

45. A pharmaceutical formulation as claimed in claim 44 in which the ratio of amoxycillin trihydrate and sodium amoxycillin is from 3:2 to 2:3.

46. A pharmaceutical formulation comprising a pharmaceutically acceptable soluble salt of amoxycillin, in a slow release phase which further comprises a release retarding excipient which is a pharmaceutically acceptable organic acid present in a molar ratio of from 100:1 to 1:10 (amoxycillin salt to organic acid).

47. A pharmaceutical formulation as claimed in claim 46 in which the molar ratio is 50:1 to 1:5.

48. A pharmaceutical formulation as claimed in claim 46 in which the organic acid is citric acid.

49. A pharmaceutical formulation as claimed in claim 46 in which the soluble salt of amoxycillin is sodium amoxycillin.

50. A kit comprising an immediate release tablet comprising amoxycillin and potassium clavulanate, optionally with a conventional (immediate release) tablet comprising amoxycillin, and a slow release tablet comprising amoxycillin (and no potassium clavulanate).

51. A pharmaceutical tablet comprising amoxycillin (as the sole active ingredient) formulated with a release retarding excipient which causes a slow release of the amoxycillin from the tablet, and excluding tablets which comprise from 400 to 500mg amoxycillin trihydrate or a mixture comprising at least 70% amoxycillin trihydrate and up to 30% sodium amoxycillin and hydroxypropyl methylcellulose.

52. A tablet as claimed in claim 51 which comprises 100 to 1250 mg amoxycillin.

53. A tablet as claimed in claim 51 in which the release retarding excipient is xanthan gum.

54. A tablet formulation as claimed in claim 51 in which the xanthan gum is pharmaceutical grade xanthan gum, 200 mesh.

55. A tablet formulation as claimed in claim 51 in which the xanthan gum is present in from 0.5 to 25% by weight.

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Abstract

Bacterial infections may be treated using a high dosage regimen of amoxycillin and potassium clavulanate. Preferably, the dosage is provided by a bilayer tablet

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Figure 1

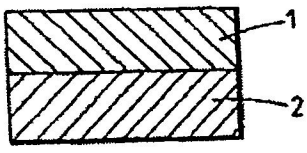


Fig. 1A

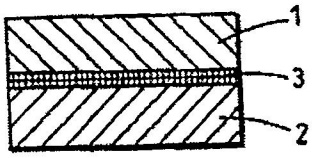


Fig. 1B

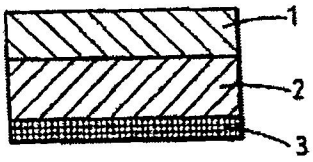


Fig. 1C

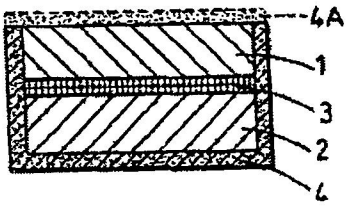


Fig. 1D

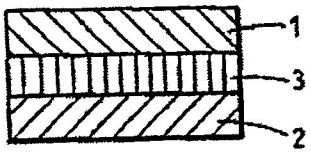
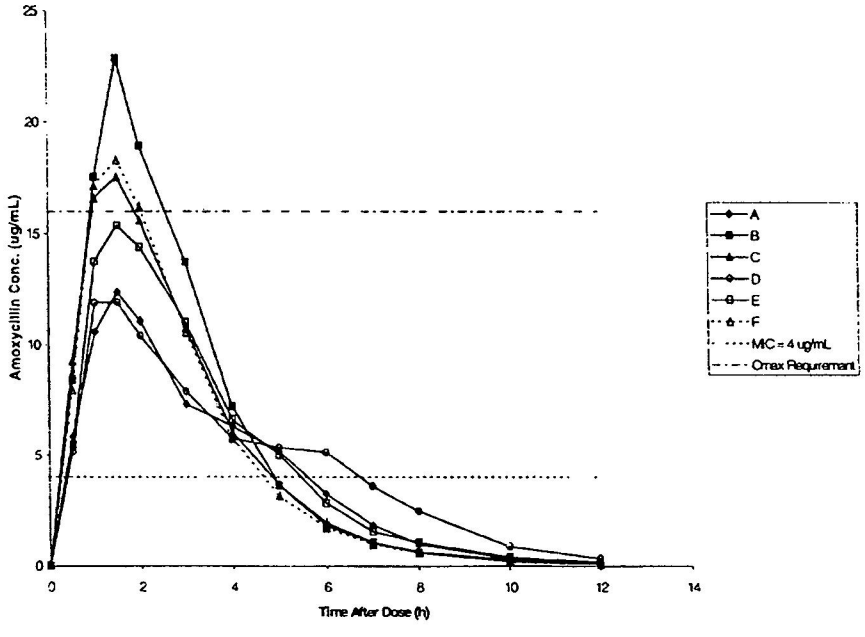


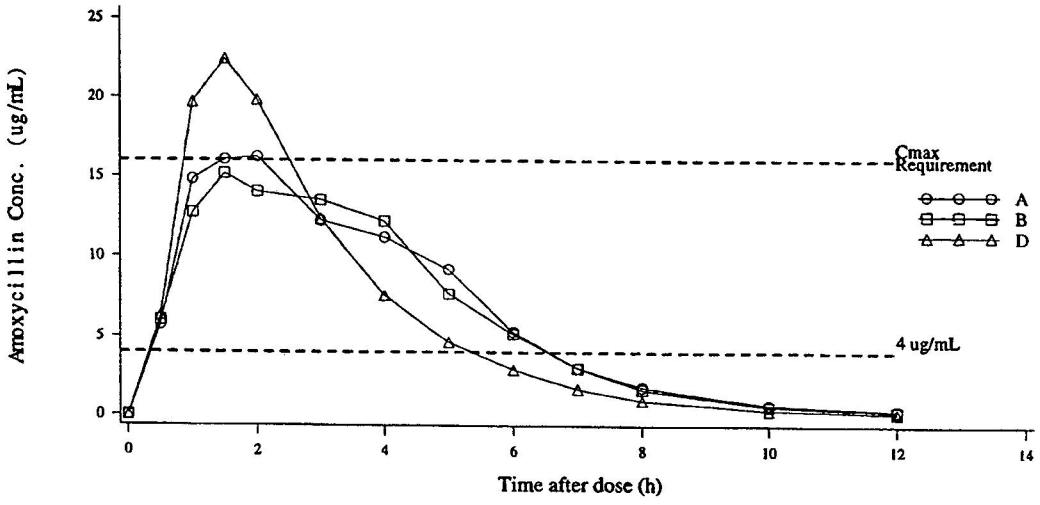
Fig. 1E

Figure 2 – Mean Amoxycillin Plasma Profiles for Study A



A is formulation I, C is formulation II, D is formulation III, E is formulation IV, F is formulation V.

Figure 3 – Mean Amoxycillin Plasma Profiles for Study B



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ESTADOS UNIDOS DE AMERICA

A TODOS AQUELLOS A QUIENES LLEGUEN LOS PRESENTES:

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Oficina de Patentes y Marcas Registradas de Estados Unidos

5 de abril de 2000

SE CERTIFICA QUE SE ADJUNTA AL PRESENTE DOCUMENTO UNA COPIA FIEL DE LOS ARCHIVOS DE LA OFICINA DE PATENTES Y MARCAS REGISTRADAS DE ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA QUE CUMPLIÓ LOS REQUISITOS PARA OTORGARLE UNA FECHA DE REGISTRO BAJO EL TITULO 35 DEL CODIGO DE ESTADOS UNIDOS NUMERAL 111.

NUMERO DE SOLICITUD: *60/150.727*

FECHA DE REGISTRO: *25 de agosto de 1999*

(Sello de oblea)

Por Autoridad del

COMISIONADO DE PATENTES Y MARCAS REGISTRADAS

(Firma ilegible)

P. SWAIN

Funcionario que Certifica

172

176

"CERTIFICADO DE CORREO EXPRESO"
Número Etiqueta Porte "Correo Expreso" *Numeración ilegible*
Fecha de Depósito: **25 de agosto, 1999**
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Firma *Firma ilegible*

HOJA DE REMISION DE SOLICITUD PROVISIONAL

Esta es una solicitud para registrar una SOLICITUD PROVISIONAL de PATENTE bajo 37 CFR 1.53©.

Causa No.	P32402P		

INVENTOR(es) / SOLICITANTE(s) Apellido	Primer Nombre	Inicial Media	Residencia (Ciudad y estado o país extranjero)
Storm	Kevin	H.	Bristol, Tennessee
Conley	Creigthon	P.	Bristol, Tennessee

TITULO DE LA INVENCION (280 caracteres máx.)
FORMULACION FARMACEUTICA

DIRECCION DE CORRESPONDENCIA
SMITHKLINE BEECHAM CORPORATION
Corporate Intellectual Property – UW2220
709 Swedeland Road
King of Prussia
Teléfono No. 610-270-5017
Fax No. 610-270-5090

Estado	PA	Código Postal	19406-2799	País	Estados Unidos de América

PARTES DE SOLICITUD ADJUNTAS (marque todo lo que aplica)

☒ Especificación	Número de páginas	23	☐ Declaración Pequeña Entidad	
☒ Dibujos	Número de hojas	1	☐ Otro (especifique)	

METODO PAGO PARA REGISTRO DERECHOS ESTA SOLICITUD PROVISIONAL DE PATENTE
☒ Por el presente documento el Comisionado está autorizado a cobrar derechos de registro y abonarlos a la Cuenta de Depósito No. **19-2570**
DERECHO POR REGISTRO PROVISIONAL ($) **$150,00**

La invención se realizó por medio de una agencia del Gobierno de los Estados Unidos o bajo contrato con una agencia del Gobierno de los Estados Unidos.
☒ No.
☐ Sí, el nombre de la agencia del gobierno de los Estados Unidos y el número del contrato son: _____

Presentado respetuosamente,
Firma: *Firma ilegible*
Dara L. Dinner
Fecha: 25 ag 99
Registro No.: **33680**

☐ Inventores adicionales nombrados en hojas numeradas por separado que aquí se adjuntan.

UNICAMENTE SOLICITUD PROVISIONAL DE REGISTRO

ENVIESE A: Comisionado Asistente para Patentes, Buzón Solicitud Provisional, Washington, D.C. 20231

Reivindicaciones

1. Una formulación de tableta que comprende amoxicilina y clavulanato de potasio donde todo el clavulanato de potasio y parte de la amoxicilina se encuentra en UNa primera fase en QUE se libera inmediatamente y el resto de la amoxicilina en una segunda fase en la cual la amoxicilina es liberada lentamente.

2. Una formulación de tableta que comprende clavulanato de potasio y una primera parte de amoxicilina formulada con excipientes farmacéuticamente aceptables que permiten la inmediata liberación del clavulanato de potasio y amoxicilina y comprende además una segunda parte de amoxicilina formulada con excipientes farmacéuticamente aceptables que permiten la lenta liberación de la amoxicilina.

3. Una formulación de tableta según la reivindicación 1 donde el perfil farmacocinético de las tabletas proporcionará un valor de amoxicilina C_{max} de al menos 12 µg/ml en el plasma humano.

4. Una formulación de tableta según la reivindicación 1 donde el perfil farmacocinético de las tabletas proporcionará una concentración media de amoxicilina en plasma de al menos 4 µg/ml durante al menos 4.4 horas.

5. Una formulación de tableta según la reivindicación 1 donde la amoxicilina y el clavulanato de potasio están presentes en una proporción por peso de 1:1 a 30:1.

6. Una formulación de tableta según la reivindicación 5 donde la amoxicilina y el clavulanato de potasio están presentes en una proporción por peso de 10:1 a 20:1.

7. Una formulación de tableta según la reivindicación 5 donde la amoxicilina y el clavulanato de potasio están presentes en una proporción por peso de 11:1 a 17:1.

8. Una formulación de tableta según la reivindicación 5 donde la amoxicilina y el clavulanato de potasio están presentes en una proporción por peso de aproximadamente 12:1, 14:1 o 16:1.

9. Una formulación de tableta según la reivindicación 1 donde la parte de amoxicilina que es liberada inmediatamente se suministra como trihidrato de amoxicilina o amoxicilina de sodio (cristalina) o una mezcla de ambos mientras que la parte de amoxicilina que es liberada lentamente se suministra como trihidrato de amoxicilina o amoxicilina de sodio (cristalina) o una mezcla de ambos.

10. Una formulación de tableta según la reivindicación 9 donde la amoxicilina se encuentra presente en las fases de liberación inmediata y lenta en una proporción de 3:1 a 1:3.

11. Una formulación de tableta según la reivindicación 10 donde la amoxicilina se encuentra presente en las fases de liberación inmediata y lenta en una proporción de 3:2 a 2:3.

12. Una formulación de tableta según la reivindicación 10 donde la amoxicilina se encuentra presente en las fases de liberación inmediata y lenta en una proporción de 3:2 a 1:1.

13. Una formulación de tableta según la reivindicación 1 que comprende amoxicilina y clavulanato de potasio en una proporción de 14:1, y comprende cerca de 438 mg de amoxicilina y cerca de 62.5 mg de clavulanato de potasio en la fase de liberación inmediata y cerca de 438 mg de amoxicilina en la fase de liberación lenta.

14. Una formulación de tableta según la reivindicación 1 que comprende amoxicilina y clavulanato de potasio en una proporción de 16:1, y comprende cerca de 563 mg de amoxicilina y cerca de 62.5 mg de clavulanato de potasio en la fase de liberación inmediata y cerca de 438 mg de amoxicilina en la fase de liberación lenta.

15. Una formulación de tableta según la reivindicación 1 donde las fases de

liberación inmediata y lenta se suministran como capas separadas de una tableta por capas.

16. Una formulación de tableta según la reivindicación 15 donde la capa de liberación lenta comprende amoxicilina junto con un excipiente retardante de liberación que permite la lenta liberación de la amoxicilina.

17. Una formulación de tableta según la reivindicación 16 donde el excipiente retardante de liberación se selecciona de polímeros sensibles al pH; un polímero retardante de liberación con un alto grado de expansión en contacto con el agua o medio acuoso; un material polimérico que forma un gel en contacto con el agua o medio acuoso; y un material polimérico que tiene ambas características, que se expande y se gelifica cuando entra en contacto con agua o un medio acuoso.

18. Una formulación de tableta según la reivindicación 17 donde el polímero retardante de liberación que se gelifica se selecciona entre metilcelulosa, carboximetilcelulosa, hidroxipropilmetilcelulosa de bajo peso molecular, polivinilalcoholes de bajo peso molecular, polioxietilenoglicoles y polivinilpirrolidona con enlace no cruzado o goma arábiga.

19. Una formulación de tableta según la reivindicación 17 donde el excipiente retardante de liberación es la goma arábiga.

20. Una formulación de tableta según la reivindicación 19 donde la goma arábiga constituye un grado de malla fina de la goma arábiga.

21. Una formulación de tableta según la reivindicación 20 donde la goma arábiga es goma arábiga de grado farmacéutico de malla 200.

22. Una formulación de tableta según la reivindicación 19 donde la goma arábiga está presente de 0.5 a 25% por peso de la capa.

23. Una formulación de tableta según la reivindicación 15 donde la capa de liberación lenta comprende de 70 a 80% de amoxicilina, de 0.5 a 25% de goma arábiga, de 10 a 30% de materiales de ayuda de llenado/compresión, y cantidades convencionales de lubricantes.

24. Una formulación de tableta según la reivindicación 23 donde la capa

de liberación lenta comprende de 70 a 80% de amoxicilina, de 1.0 a 15% de goma arábiga, de 15 a 30% de celulosa microcristalina, y de 0.5 a 1.5% de estearato de magnesio.

25. Un juego que comprende una tableta de liberación inmediata que contiene amoxicilina y clavulanato de potasio, opcionalmente con una tableta convencional (liberación inmediata) que contiene amoxicilina, y una tableta de liberación lenta que contiene amoxicilina (sin clavulanato de potasio).

26. Una formulación de tableta que contiene amoxicilina (como único ingrediente activo) formulada con un excipiente retardante de liberación que causa una liberación lenta de la amoxicilina de la tableta, y excluye las tabletas que contiene de 400 a 500 mg de trihidrato de amoxicilina o una mezcla que comprende al menos un 70% de trihidrato de amoxicilina y hasta un 30% de amoxicilina de sodio e hidroxipropil metilcelulosa.

27. Una tableta según la reivindicación 26 que comprende de 100 a 1250 mg de amoxicilina.

28. Una tableta según la reivindicación 26 donde el excipiente retardante de liberación es goma arábiga.

29. Una formulación de tableta según la reivindicación 26 donde la goma arábiga es goma arábiga de grado farmacéutico malla 200.

30. Una formulación de tablet según la reivindicación 26 donde la goma arábiga Está presente en 0.5 a 25% por peso de la capa.

31. Un método de tratamiento de las infecciones bacterianas en humanos que comprende la administración de una cantidad terapéuticamente efectiva de amoxicilina y clavulanato de potasio en una formulación de tableta que comprende una primera fase en la que todo el clavulanato de potasio y parte de la amoxicilina son liberados inmediatamente y una segunda fase que comprende el resto de la amoxicilina de la cual la amoxicilina se libera lentamente.

32. Un método según la reivindicación 31 donde la infección es causada por los

organismos *S pneumoniae* (incluido el *S pneumoniae* resistente a medicamentos), *H influenzae* y/o *M catarrhalis*.

33. Un método según la reivindicación 31 donde la formulación de tableta se toma en intervalos de dosificación de 12 horas.

34. Una formulación farmacéutica que comprende 1000 mg ± 5% de amoxicilina y 62.5 mg ± de ácido clavulánico de potasio, en un proporción nominal de aproximadamente 16:1, en combinación con excipientes o portadores farmacéuticamente aceptables.

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PA 229234

THE UNITED STATES OF AMERICA

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United States Patent and Trademark Office

April 05, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/150,727***
FILING DATE: ***August 25, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

P. SWAIN
Certifying Officer

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08/25/99 JC572 U.S. PTO

JC526 U.S. PTO 60/150727 08/25/99

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

Docket No.	P32402P		

INVENTOR(s) / APPLICANT(s)

Last Name	First Name	Middle Initial	Residence (City and Either State or Foreign Country)
Storm	Kevin	H.	Bristol, Tennessee
Conley	Creigthon	P.	Bristol, Tennessee

TITLE OF THE INVENTION (280 characters max)

PHARMACEUTICAL FORMULATION

CORRESPONDENCE ADDRESS

SMITHKLINE BEECHAM CORPORATION
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709 Swedeland Road
King of Prussia

Telephone No. 610-270-5017
Facsimile No. 610-270-5090

State	PA	Zip Code	19406-2799	Country	United States of America

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of Pages	23	☐ Small Entity Statement	
☒ Drawings	Number of Sheets	1	☐ Other (specify)	

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 19-2570	PROVISIONAL FILING FEE AMOUNT ($)	$150.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:_____.

Respectfully submitted,
Signature: Date: 25 Aug 99
Dara L. Dinner Registration No.: 33,680

o Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

SEND TO: Assistant Commissioner for Patents, Box Provisional Application, Washington, D.C. 20231.

Pharmaceutical Formulation

Field of the Invention

This invention relates to novel tablet formulations for oral administration of amoxycillin and potassium clavulanate.

Background of the Invention

Amoxycillin and potassium clavulanate are respectively a known β-lactam antibiotic and a known β-lactamase inhibitor. Products comprising amoxycillin and potassium clavulanate are marketed under the trade name "Augmentin" by SmithKline Beecham. Such products are particularly effective for treatment of community acquired infections, in particular respiratory tract infections in adults and otitis media in children.

Various tablet formulations of amoxycillin and clavulanate have been approved for marketing, comprising various different weights and ratios of amoxycillin and clavulanate, for instance, conventional swallow tablets comprising 250/125, 500/125, 500/62.5, 875/125 mg amoxycillin/clavulanate. Such tablets comprise amoxycillin and clavulanate in the ratio 2:1, 4:1, 8:1 and 7:1, respectively . The 875/125 mg tablet was developed to provide a tablet formulation which could be administered in a bid (twice daily) dosage regimen It is also marketed for tid (three times daily) dosing, in Italy and Spain. The 500/62.5 mg tablet was also developed to provide a tablet formulation which could be administered in a tid dosage regimen, two such tablets being taken every 12 hours (hereinafter "h"), in preference to a single 1000/125 mg tablet. A 1000/125 mg single dosage is also available, in France, but as a sachet rather than a single tablet.

In addition, WO 97/09042 (SmithKline Beecham) describes tablet formulations comprising amoxycillin and clavulanate in a ratio in the range 12:1 to 16:1, preferably 14:1 ratio. Furthermore, it is suggested that the preferred unit dosage of 1750/125 mg may be provided as two tablets, the first comprising 875/125 mg amoxycillin and clavulanate and the second 875 mg amoxycillin. The 14:1 ratio is said to be useful for the empirical treatment of bacterial infection potentially caused by drug resistant *S pneumoniae* (DRSP). This patent application also describes paediatric formulations comprising amoxycillin and clavulanate in a 14:1 ratio, for administering amoxycillin dosages of 90 mg/kg/day. Data suggest that such a dosage may provide antibiotic

concentrations sufficient to eradicate DRSP with MICs ≤ 4 μg/ml (Bottenfield et al, Pediatric Infect Dis J, 1998, 17, 963-8).

WO 94/16696 (SmithKline Beecham) discloses generally that clavulanate may unexpectedly enhance the efficacy of amoxycillin against microorganisms having a resistant mechanism which is not β–lactamase mediated.

Existing marketed tablet formulations of amoxycillin and potassium clavulanate are conventional in that they provide immediate release of the active ingredients once the tablet reaches the stomach. There has also been some interest in developing formulations in which the release profile is modified, to allow for a longer interval between dosages, for instances, every 12 hours (bid, q12h), rather than every 8 hours (tid, q8h).

Thus, for instance, WO 95/20946 (SmithKline Beecham) describes layered tablets comprising amoxycillin and, optionally, clavulanate, having a first layer which is an immediate release layer and a second layer which is a slow release layer. The broadest ratio of amoxycillin to clavulanate is 30:1 to 1:1, with a preferred range of 8:1 to 1:1. Amoxycillin is suitably in the form of amoxycillin trihydrate. Examples provided of such bilayered tablets have amoxycillin trihydrate in the immediate release layer and amoxycillin plus clavulanate in the slow release layer. Multi-layered tablets are described more generically in WO 94/06416 (Jagotec AG).

In addition, WO 95/28148 (SmithKline Beecham) describes amoxycillin/potassium clavulanate tablet formulations having a core containing amoxycillin and potassium clavulanate coated with a release retarding agent and surrounded by an outer casing layer of amoxycillin and potassium clavulanate. The release retarding agent is an enteric coating, so that there is a immediate release of the contents of the outer core, followed by a second phase from the core which is delayed until the core reaches the intestine.

Furthermore, WO 96/04908 (SmithKline Beecham) describes amoxycillin/potassium clavulanate tablet formulations which comprise amoxycillin and potassium clavulanate in a matrix, for immediate release, and granules in a delayed release form comprising amoxycillin and potassium clavulanate. Such granules are coated with an enteric coating, so release is delayed until the granules reach the intestine.

In addition, WO 94/27557 (SmithKline Beecham) describes controlled release formulations of amoxycillin and clavulanic acid prepared using a hydrophobic waxy material which is then subjected to thermal infusion.

Controlled release formulation comprising amoxycillin has been described by Hoffman *et al*, (Journal of Controlled Release, 1998, 54, 29-37 and WO 98/22091) and

Hilton et al (Journal of Pharmaceutical Sciences, 1993, 82, 737-743). Hoffman et al describe a tablet comprising 500 mg of amoxycillin in a matrix comprising hydroxypropyl methyl cellulose, designed to release 50% of its contents in the first three hours and complete the drug release process over eight hours. The time above MIC was found to be significantly extended, compared to a capsule formulation, but not enough for a 12 h dosing interval. The discussion is in the context of a theoretical MIC of 0.2 µg/ml. In contrast, Hilton *et al* failed to show an advantage over a conventional capsule. Part of the challenge in providing formulations of amoxycillin in which the drug release is effectively modified is the relatively narrow window for absorption of the drug in the small intestine and the relatively short half life of the drug.

Controlled release formulations comprising from 7.5 to 25% xanthan gum are described in EP 0 234 670-A (Boots Co. plc). The preferred embodiment is a tablet comprising ibuprofen as the drug substance and 15-20% xanthan gum, which is taken once daily.

In existing tablet formulations, amoxycillin is present in the form amoxycillin trihydrate, as the use of this form provides tablets with greater storage stability than those in which amoxycillin is present as sodium amoxycillin (see GB 2 005 538, Beecham Group Ltd). Sodium amoxycillin is however used as the amoxycillin component in existing formulations of amoxycillin and potassium clavulanate adapted for IV administration. The form of sodium amoxycillin used is a spray-dried form. A further form of sodium amoxycillin, crystalline sodium amoxycillin, is described in EP 0 131 147-A1 (Beecham Group plc). Sodium amoxycillin is relatively water soluble in comparison to amoxycillin trihydrate.

Of concern is the increasing resistance of pathogenic organisms such as those found in respiratory tract infections to anti-infective agents such as amoxycillin/clavulanate, in particular drug resistant *S pneumoniae*. Increased resistance to penicillin of *S pneumoniae* (due to penicillin binding proteins) has recently developed around the world and has affected clinical outcomes (see for instance Applebaum P C, Ped Inf Dis J, 1996, 15(10), 932-9). These resistant *S pneumoniae* have been termed "DRSP" as they often exhibit decreased susceptibility across a wide range of antimicrobial classes, including macrolides, azalides, beta-lactams, sulfonamides and tetracyclines. Amoxycillin (with or without clavulanate), along with some of the newer quinolones, has remained among the most active oral drugs against the increasingly resistant isolates of *S pneumoniae*, based on both MIC levels and pharmacokinetic properties of these compounds. Resistance rates (and MICs) have however continued to increase. Susceptible *S pneumoniae* have an MIC of ≤ 2 µg/ml, Intermediate resistance is been defined as an MIC in the range 0.12 to 1.0 µg/ml whilst

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Penicillin resistance is defined as an MIC of ≥ 2 μg/ml. There is a consequently a need to provide new formulations of amoxycillin/clavulanate that combine the known safety profile and broad spectrum with improved activity against DRSP with higher MICs in empiric therapy settings where *H influenzae* and *M catarrhalis* can be anticipated to be co-pathogens.

Summary of the Invention

The present invention is directed to a tablet formulation comprising amoxycillin and potassium clavulanate in which all of the potassium clavulanate and part of the amoxycillin is in a first phase from which it is immediately released and the remainder of the amoxycillin in a second phase from which the amoxycillin is slowly released.

In a preferred embodiment the tablet formulation comprises potassium clavulanate and a first part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for immediate release of the potassium clavulanate and amoxycillin and further comprise a second part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for slow release of amoxycillin.

Preferably the tablet formulation has a pharmacokinetic profile in which the tablets will provide an amoxycillin C_{max} value in human plasma of at least 12 μg/ml, and more preferably at least 4 μg/ml for at least 4.4 hours.

Brief Description of the Drawings

Figures 1A to 1E show the structure (longitudinal section) of various types of compressed tablet formulation of the present invention.

Detailed Description of the Invention

For β–lactams, including amoxycillin, it is recognised time above minimum inhibitory concentration (T > MIC) is the pharmacodynamic parameter most closely related to efficacy. For a variety of β–lactams, a bacteriological cure rate of 85 to 100% is achieved when serum concentrations exceed the MIC for more than about 40% of the dosing interval (Craig and Andes, Ped Inf Dis J, 1996, 15, 255-259) For a 12 hour dosing interval, this is about 4.8 hours. In addition, it is also necessary to provide a plasma C_{max} value well above the MIC value and it has been suggested that the C_{max} value should be at least three times, if not four times, the MIC value.

In a clinical study using the existing Augmentin 875/125 mg tablet, it was found that, when dosed at 12 hour intervals, the time above MIC was about 40% for an MIC of 2 μg/ml but only about 30% for an MIC of 4 μg/ml. The existing Augmentin

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875/125 mg tablet has a C_{max} value of 11.6±2.8 μg/ml (Physicians Desk Reference, Medical Economics Co, 52 edition, 1998, 2802).

It has now been found that an improved pharmacokinetic profile may be achieved by providing the amoxycillin component in two phases.

Accordingly in a first aspect, the present invention provides for a tablet formulation comprising amoxycillin and potassium clavulanate in which all of the potassium clavulanate and part of the amoxycillin is in a first phase from which it is immediately released and the remainder of the amoxycillin in a second phase from which the amoxycillin is slowly released.

In a further aspect, the present invention provides for a tablet formulation comprising potassium clavulanate and a first part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for immediate release of the potassium clavulanate and amoxycillin and further comprising a second part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for slow release of amoxycillin.

In tablets of the present invention, potassium clavulanate is released substantially immediately from the tablet, when the tablet reaches the stomach and is absorbed therefrom, thereby minimising the risk of degradation from prolonged exposure to the stomach. The amoxycillin release profile is made up of a contribution from the immediate release component. This is then complemented and extended by an on-going contribution from the slow release component.

As used herein, the term "immediate release" refers to the release of the majority of the active material content within a relatively short time, for example within 1 hour, preferably within 30 minutes, after oral ingestion.

As used herein, the term "slow release" refers to the gradual but continuous or sustained release over a relatively extended period of the active material content (in this case amoxycillin) after oral ingestion and which starts when the tablet reaches the stomach and starts to disintegrate/dissolve. The release will continue over a period of time and may continue through until and after the tablet reaches the intestine. This can be contrasted with the term "delayed release" in which release of the active does not start immediately the tablet reaches the stomach but is delayed for a period of time, for instance until when the tablet reaches the intestine when the increasing pH is used to trigger release of the active from the tablet.

The term "amoxycillin" is used generically to refer to both amoxycillin trihydrate and (crystalline) sodium amoxycillin, without distinction.

Unless otherwise indicated, weights of amoxycillin and clavulanate refer to the equivalent weights of the corresponding free acids. In addition, it will be appreciated

that in practice, weights of amoxycillin and clavulanate to be incorporated into a formulation will be further adjusted, in accord with conventional practice, to take account of the potency of the amoxycillin and clavulanate.

Preferably, the pharmacokinetic profile of tablets of the present invention will provide a mean C_{max} value for amoxycillin in human plasma of at least 12 μg/ml, preferably 16 μg/ml. In addition, tablets of the present invention will preferably have a mean plasma concentration f ≥4 μg/ml of amoxycillin for at least 4.4h, preferably at least 4.5h, more preferably at least 4.8h, yet more preferably between 5 and 7h. Preferably, the tablets will have a biphasic profile. Such a profile is determined for a unit dosage of the formulation which may be provided in one or more, for instance one or two, tablets. Preferably, a tablet of the present invention will have an AUC value which is substantially similar, for instance at least 80%, preferably at least 90%, to that of the corresponding dosage of amoxycillin taken as a conventional (immediate release) tablet, over the same dosage period, thereby maximising the absorption of the amoxycillin component from the slow release component. Plasma concentrations of amoxycillin can be readily determined in blood samples taken from patients according to procedures well known and documented in the art.

Preferably, in tablets of the present invention, amoxycillin and potassium clavulanate are present in a ratio by weight of from 1:1 to 30:1, more preferably 10:1 to 20:1, yet more preferably 11:1 to 17:1, even more preferably 13:1 to 16:1. Representative ratios include about 12:1, about 14:1 or about 16:1.

In tablets of the present invention, the portion of amoxycillin which is released immediately is provided as amoxycillin trihydrate or (crystalline) sodium amoxycillin or a mixture thereof, preferably amoxycillin trihydrate, whilst the portion of amoxycillin which is released slowly is provided as amoxycillin trihydrate or (crystalline) sodium amoxycillin or a mixture thereof. Preferably, amoxycillin is present in the immediate and slow release phases in a ratio of from 3:1 to 1:3, more preferably, from 3:2 to 2:3, yet more preferably 3:2 to 1:1. Representative ratios include about 2:1, 9:7 or 1:1. It may be found useful to employ an excess of amoxycillin in the immediate release phase, to ensure an adequate C_{max} value.

A representative tablet of the present invention comprises amoxycillin and potassium clavulanate in a 14:1 ratio, and comprises about 438 mg amoxycillin and about 62.5 mg of potassium clavulanate in the immediate release phase and about 438 mg of amoxycillin in the slow release phase, providing overall an 875/62.5 mg tablet.

A further representative tablet of the present invention comprises amoxycillin and potassium clavulanate in a 16:1 ratio, and comprises about 563 mg amoxycillin and

about 62.5 mg of potassium clavulanate in the immediate release phase and about 438 mg of amoxycillin in the slow release phase, providing overall an 1000/62.5 mg tablet.

A further representative tablet of the present invention comprises amoxycillin and potassium clavulanate in a 12:1 ratio, and comprises about 500 mg amoxycillin and about 62.5 mg of potassium clavulanate in the immediate release phase and about 250 mg of amoxycillin in the slow release phase, providing overall a 750/62.5 mg tablet.

It will be appreciated that such 1000/62.5 mg tablets are novel. Accordingly, in a further aspect, the present invention provides for a pharmaceutical formulation comprising 1000 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanic acid, in a nominal ratio of about 16:1, in combination with pharmaceutically acceptable excipients or carriers. Such formulations may be presented as tablets or single dosage sachets. Conventional (immediate release) 1000/62.5 mg tablets and sachets can be readily prepared by adapting compositions previously described for 875/125 and 1000/125 mg tablets (see for instance, WO 95/28927, WO 98/35672, SmithKline Beecham).

It will be further appreciated that such 750/62.5 mg tablets are novel. Accordingly, in a further aspect, the present invention provides for a pharmaceutical formulation comprising 750 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanic acid, in a nominal ratio of about 12:1, in combination with pharmaceutically acceptable excipients or carriers. Such formulations may be presented as tablets or single dosage sachets. Conventional (immediate release) 750/62.5 mg tablets and sachets can be readily prepared by adapting compositions previously described for 500/125, 875/125 and 1000/125 mg tablets (see for instance, WO 95/28927, WO 98/35672, SmithKline Beecham).

The immediate and slow release phases for tablets of the present invention may be provided in a number of different formats.

In a preferred aspect, the immediate and slow release phases are provided as separate layers of a layered tablet. Layered tablets comprising amoxycillin and potassium clavulanate have been previously described (WO 95/20946 (SmithKline Beecham).

Accordingly, in a further aspect, the present invention provides for a tablet formulation comprising potassium clavulanate and amoxycillin in an immediate release layer phase and amoxycillin in a slow release layer.

An immediate release layer may be, for example, a layer which disintegrates immediately and has a composition similar to that of known tablets which disintegrates immediately. For example, the layer may comprise in addition to the active material content, excipients including binders such as povidone (polyvinylpyrrolidone), for

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instance the product Plasdone K29-32 (trade mark, ISP, 1361 Alps Road, Wayne, NJ, USA); compression aids; fillers or diluents such as mannitol, microcrystalline cellulose and silicon dioxide, for instance the product Syloid (trade mark); disintegrants such as sodium starch glycollate, for instance the product Explotab (trade mark, FMC Corp, 1735 market Street, Philadelphia, PA, USA), microcrystalline cellulose, for instance the product Avicel (trade mark, Grace); lubricants such as talc or magnesium stearate; etc. Such a immediate release layer may comprise around 30 - 70 % (all percentages given herein are on a weight percentage basis unless otherwise stated), preferably 50-60% of active material content, around 10 - 30% of fillers/compression aids, and conventional amounts of disintegrants and lubricants etc.

An alternative type of immediate release layer may be a swellable layer having a composition which incorporates polymeric materials which swell immediately and extensively in contact with water or aqueous media, to form a water permeable but relatively large swollen mass. Active material content may be immediately leached out of this mass.

Slow release layers have a composition which comprises amoxycillin together with a release retarding excipient which allows for slow release of amoxycillin. Suitable release retarding excipients include pH sensitive polymers, for instance polymers based upon methacrylic acid copolymers such as the Eudragit (trade mark) polymers, for example Eudragit L (trade mark) which may be used either alone or with a plasticiser; release-retarding polymers which have a high degree of swelling in contact with water or aqueous media such as the stomach contents; polymeric materials which form a gel on contact with water or aqueous media; and polymeric materials which have both swelling and gelling characteristics in contact with water or aqueous media.

Release retarding polymers which have a high degree of swelling include, *inter alia*, cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethylamide, potassium methacrylatedivinylbenzene co-polymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone, high-molecular weight polyvinylalcohols, etc.

Release retarding gellable polymers include methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, low-molecular weight polyvinylalcohols, polyoxyethyleneglycols, non-cross linked polyvinylpyrrolidone, xanthan gum etc.

Release retarding polymers simultaneously possessing swelling and gelling properties include medium-viscosity hydroxypropylmethylcellulose and medium-viscosity polyvinylalcohols.

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A preferred polymer is xanthan gum, in particular a fine mesh grade of xanthan gum, preferably pharmaceutical grade xanthan gum, 200 mesh, for instance the product Xantural 75 (also known as Keltrol CR, Trade Mark, Monsanto, 800 N Lindbergh Blvd, St Louis, MO 63167, USA). Xanthan gum is a polysaccharide which upon hydration forms a viscous gel layer around the tablet through which the active has to diffuse. It has been shown that the smaller the particle size, the slower the release rate. In addition, the rate of release of drug substance is dependent upon the amount of xanthan gum used and can be adjusted to give the desired profile.

Examples of other polymers which may be used include Methocel K4M (Trade Mark), Methocel E5 (Trade Mark), Methocel E5O (Trade Mark), Methocel E4M (Trade Mark), Methocel K15M (Trade Mark) and Methocel K100M (Trade Mark). An example of a suitable polymer mixture is a mixture of Methocel E5 and K4M, for example 1:1, w:w.

Other known release-retarding polymers which may be incorporated include hydrocolloids such as natural or synthetic gums, cellulose derivatives other than those listed above, proteinaceous substances such as acacia, gum tragacanth, locust bean gum, guar gum, agar, pectin, carageenam, soluble and insoluble alginates, carboxypolymethylene, gelatin, casein, zein, Veegum (trade mark) and the like.

Such a slow release layer may contain polymers which immediately swell in contact with water or aqueous media so that they form a relatively large swollen mass which is not immediately discharged from the stomach into the intestine.
The slow release layer may also include fillers/compression aids such as microcrystalline cellulose, for instance the product Avicel (trade mark); desiccants, such as silicon dioxide, for instance the product Syloid (trade mark); disintegrants, such as sodium starch glycollate, for instance the product Explotab (trade mark); binders such as povidone (polyvinylpyrrolidone) for instance the product Plasdone K3O (trade mark); lubricants such as talc or magnesium stearate, pH-controlling agents such as potassium dihydrogen phosphate or substantially insoluble ion-exchange resins, and soluble excipients such as mannitol or other soluble sugars.

When xanthan gum is used as release-retarding polymer, the layer contains from 70 to 80% of amoxycillin, from 0.5 to 25%, preferably 1.0 to 15%, more preferably 4 to 10% of xanthan gum, from 10 to 30%, preferably 15 to 30% of fillers/compression aids, and conventional quantities of lubricants. In a preferred embodiment, the slow release layer comprises from 70 to 80% of amoxycillin, from 1.0 to 5%, of xanthan gum, from 15 to 30% of microcrystalline cellulose, and from 0.5 to 1.2% of magnesium stearate.

When release-retarding polymers other than xanthan gum are used, the slow release layer may contain around 30 to 70%, preferably from 40 to 60%, of amoxycillin,

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from 15 to 45% of release-retarding polymer, from 0 to 30% of fillers/compression aids, conventional quantities of disintegrants and lubricants, and from 5 - 20% of soluble excipients.

Alternative types of slow-release layers are those in which the active material content is mixed with, coated with, or embedded in, a matrix of a poorly soluble or practically insoluble excipient (e.g. calcium phosphate etc) and/or a hydrophobic excipient (e.g. fats or waxes). Poorly soluble or practically insoluble excipients can yield a very hard tablet which would slowly dissolve or erode from the surface without substantial diffusion of surrounding liquid into the body of the tablet. Hydrophobic excipients similarly hinder moisture ingress and release of active material content occurs through erosion and enzymatic digestion. Examples of such waxes include Compritol (trade mark), for instance, Compritol HD5 and Compritol 888 (trade marks). Compritol wax remains intact in aqueous solutions at all pH, but is digested by lipase enzymes at pH 5-7. Thus active material content such as clavulanate protected with Compritol wax as described above may be released primarily in the small intestine due to the action of intestinal lipase. Typically when the slow- or delayed- release layer includes such a wax, the wax may suitably comprise 10-80% of the layer, e.g. around 20-40%, e.g. 30% ± 5% by weight.

The tablet formulations of the invention may also include one or more barrier layers, which may be located between the respective first and second layers, and/or on one or more of the outer surfaces of the first and second layers, for example the end faces of the layers of a substantially cylindrical tablet. Such barrier layers may, for example, be composed of polymers which are either substantially or completely impermeable to water or aqueous media, or are slowly erodable in water or aqueous media or biological liquids and/or which swell in contact with water or aqueous media. Suitably the barrier layer should be such that it retains these characteristics at least until complete or substantially complete transfer of the active material content to the surrounding medium.

Suitable polymers for the barrier layer include acrylates, methacrylates, copolymers of acrylic acid, celluloses and derivatives for the barrier layer such as ethylcelluloses, cellulose acetate propionate, polyethylenes and polyvinyl alcohols etc. Barrier layers comprising polymers which swell in contact with water or aqueous media may swell to such an extent that the swollen layer forms a relatively large swollen mass, the size of which delays its immediate discharge from the stomach into the intestine. The barrier layer may itself contain active material content, for example the barrier layer may be a slow or delayed release layer. Barrier layers may typically have an individual thickness of 2mm to 10 microns.

Suitable polymers for barrier layers which are relatively impermeable to water include the Methocel (trade mark) series of polymers mentioned above, for example Methocel K100M, Methocel K15M, Methocel E5 and Methocel E50, used singly or combined, or optionally combined with an Ethocel (trade mark) polymer. Such polymers may suitably be used in combination with a plasticiser such as hydrogenated castor oil. The barrier layer may also include conventional binders, fillers, lubricants and compression acids etc such as Polyvidon K30 (trade mark), magnesium stearate, and silicon dioxide, e.g. Syloid 244 (trade mark).

The tablet formulation of the invention may be wholly or partly covered by a coating layer, which may be a protective layer to prevent ingress of moisture, or damage to the tablet. The coating layer may itself contain active material content, and may for example by an immediate release layer, which immediately disintegrates in contact with water or aqueous media to release its active material content, for example amoxycillin and potassium clavulanate.

As well as active material content etc, the tablet of the invention may also include a pH modifying agent, such as a pH buffer, which may be contained in either the immediate-, or slow-release layers, or in a coating around all or part of the tablet. A suitable buffer is calcium hydrogen phosphate.

In a tablet without a barrier layer, the immediate release layer comprises form 50 to 60% and the slow release layer comprises from 40 to 50% of the overall tablet weight.

When a barrier layer is present, the immediate release layer typically comprises from 40 to 50%, the slow release layer comprises from 35 to 45%, and the barrier layer comprises from 5 to 20% of the overall tablet weight.

Suitably the tablet formulations of the invention may be formed by known compression tabletting techniques for example using a known multi-layer tabletting press. Suitably a dry densification process may be used, e.g. briquetting. Typically the active material content, pH modifiers, buffers, fillers and/or diluent, release retarding agents, disintegrants and binders, when used are mixed, then lubricants and compression aids are added. The complete mixture may then be compressed under high pressure in the tablet press. Roller compaction may be used to form granulates for compaction. Alternatively wet granulation may be used, isopropanol being a suitable solvent. A suitable wet granulating aid is Polyvidon K-30 (trade mark).

For making up layers which include a wax, e.g. Compritol (trade mark) dry compression or wet granulation may be used. Typically for wet granulation a colloidal solution or suspension of the wax in a solvent such as dichloromethane may be used. Typically the solution or suspension may be mixed with the layer ingredients and the

wet cake sieved and dried. This can be repeated until the required amount of wax has been incorporated.

The barrier layer may typically be made up by a wet granulation technique, or by dry granulation techniques such as roller compaction. Typically the barrier material, e.g. Methocel (trade mark) is suspended in a solvent such as ethanol containing a granulation acid such as Ethocel or Polyvidon K-30 (trade mark), followed by mixing, sieving and granulation. Typically a first layer may be formed, then a barrier layer deposited upon it, e.g. by compression, spraying or immersion techniques, then the second layer may be formed so that the barrier layer is sandwiched between the first and second layers. Additionally or alternatively the first and second layers may be formed and a barrier layer may then be formed, e.g. by compression, spraying or immersion, on one or more of the end faces of the tablet.

Potassium clavulanate is known to be extremely water sensitive. Therefore tablet formulations which contain potassium clavulanate should be made up in dry conditions, preferably at 30% relative humidity or less, and the ingredients of the formulation should be pre-dried where appropriate. Tablet formulations of the invention should be stored in containers which are sealed against the ingress of atmospheric moisture.

The invention also provides a method for the manufacture of a tablet formulation as described above comprising the steps of forming said first and second layers, and any barrier layers and coating layer(s) which may be present.

In addition to the multilayered tablet approach hereinbefore described, other types of tablet may be used to provide an immediate release phase and a slow release phase, using the excipients hereinbefore described but providing the phases in different formats. Thus, the slow release phase may form the core of a tablet which is then surrounded by an outer casing forming the immediate release phase, optionally with an intermediate coating layer around the core and/or a final coating layer around the outer casing (see WO 95/28148, SmithKline Beecham). The slow release phase may also be provided as granules which are dispersed in a matrix of amoxycillin and potassium clavulanate, the matrix forming the immediate release phase (see WO 96/04908, SmithKline Beecham). In a further variant, a tablet may be prepared from slow release granules comprising amoxycillin and immediate release granules comprising amoxycillin and potassium clavulanate (as described in WO 92/19227, SmithKline Beecham) or immediate release granules comprising amoxycillin and potassium clavulanate, for instance in a 2:1 ratio, and further immediate release granules comprising amoxycillin (as described in WO 98/35672, SmithKline Beecham

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Laboratoires Pharmaceutiques), the granules being combined with extragranular excipients to form tablets.

In a further embodiment, the slow release phase may be provided as a separate tablet, so that the unit dosage is provided as a combination of a conventional tablet in which amoxycillin and potassium clavulanate are released immediately, optionally with a conventional amoxycillin tablet, and a tablet comprising amoxycillin (and no potassium clavulanate) from which amoxycillin is released slowly. The weight of potassium clavulanate and the combined weights of amoxycillin in the conventional and slow release tablets will provide the overall unit dosage. Thus, for instance a dosage of 1750/125 mg may be provided by an existing 875/125 mg tablet (as described in WO 95/28927, SmithKline Beecham) in combination with a slow release tablet comprising 875 mg of amoxycillin. In addition, a dosage of 1500/125 mg may be provided by an existing 500/125 mg tablet and an existing 500 mg tablet of amoxycillin in combination with a slow release tablet comprising 500 mg of amoxycillin. Accordingly, in a further aspect, the present invention provides for a kit comprising a conventional (immediate release) tablet comprising amoxycillin and potassium clavulanate, optionally with a conventional (immediate release) tablet comprising amoxycillin, and a slow release tablet comprising amoxycillin (and no potassium clavulanate).

Slow release tablets comprising amoxycillin are novel. Accordingly, in a further aspect, the present invention provides for a pharmaceutical tablet comprising amoxycillin (as the sole active ingredient) formulated with a release retarding excipient which cause a slow release of the amoxycillin from the tablet, and excluding tablets which comprise from 400 to 500 mg amoxycillin trihydrate or a mixture comprising at least 70% amoxycillin trihydrate and up to 30% sodium amoxycillin and hydroxypropyl methylcellulose.

Such tablets may comprise from 100 to 1250 mg amoxycillin which may be amoxycillin trihydrate or crystalline sodium amoxycillin or a mixture thereof, for instance 500, 875 or 1000 mg amoxycillin. Suitable excipients for slow release are those hereinbefore described for slow release layers. The tablet may comprise from 0.5 to 25%, preferably from 1 to 15%, more preferably 4 to 10% of xanthan gum, or from 10 to 25, preferably 15 to 20% of a hydroxypropylmethyl cellulose, for instance Methocel K100LV or Methocel K4M

The invention further provides a formulation as described above for use as a therapeutic substance for oral administration for the treatment of bacterial infections.

The invention further provides for the use amoxycillin and potassium clavulanate as hereinbefore described in the manufacture of a medicament for the treatment of bacterial infections.

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The invention further provides a method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxycillin and potassium clavulanate included in a formulation as described herein.

Bacterial infections amenable to tablets of the present invention include infections caused by the organisms *S pneumoniae* (including Drug Resistant *S pneumoniae*, for instance Penicillin Resistant *S pneumoniae*), and/or the β–lactamase producing respiratory pathogens, most notably *H influenzae* and *M catarrhalis*, such as respiratory tract infections, including community acquired pneumoniae (CAP), exacerbations of chronic bronchitis (AECB) and acute bacterial sinusitis (ACB), where the higher break points achievable through the improved pharmacokinetic profile will be especially advantageous compared to existing antibacterial agents. Most outpatient respiratory infections are caused by either *S pneumoniae* and/or the β–lactamase producing bacteria and are treated empirically so there is a continuing need for a drug, such as the present invention, that has a spectrum of activity that covers all such pathogens. DRSP is defined as *S pneumoniae* isolates with penicillin MICs ≥ 0.12 μg/ml.

Tablet formulations according to the present invention may be taken at dosage intervals of 12h. The unit dosage preferably comprises from 1400 to 2200 mg amoxycillin and a *pro rata* amount of clavulanate, preferably to give a ratio 13:1 to 17:1, more preferably from 1450 to 2100 mg amoxycillin. Typical unit dosages include 1750/125 mg or 2000/125 mg amoxycillin/clavulanate, which may be conveniently provided as two tablets each comprising 875/62.5 mg or 1000/62.5 mg amoxycillin/clavulanate, respectively. A further unit dosage includes 1500/125 mg amoxycillin/clavulanate which may be conveniently provided as two tablets each comprising 750/62.5 mg amoxycillin/clavulanate.

The invention will now be described by way of example only with reference to the accompanying drawings, in which:

Fig. 1 shows the structure of various types of tablet formulation of the present invention.

Referring to Fig 1, substantially cylindrical compressed tablets of the present invention are shown in longitudinal section. In Fig 1A, the tablet comprises a first layer (1) and a second layer (2), without any barrier layer or coating layer. In Fig 1B, the tablet comprises a first layer (1), a second layer (2), and a barrier layer (3) sandwiched between the first and second layers (1) and (2). In Fig 1C, the tablet comprises a first layer (1), a second layer (2), and a barrier layer (3) located on the end face of the second layer (2). In Fig 1D, the tablet comprises a first layer (1), a second layer (2), a barrier

layer (3) sandwiched between the first and second layers (1) and (2), and a coating layer (4) which partly covers the tablet. The dotted line shows the possibility of the coating layer (4A) covering the entire tablet. In Fig. 1E, the tablet comprises a first layer (1) a second layer (2), and a third layer (3) intermediate between the first and second layers (1) and (2). All three of these layers (1), (2) and (3) include active material content.

Formulations for an amoxycillin slow release tablet

875 mg Crystalline Sodium Amoxycillin Tablets with Xanthan Gum, 200 mesh.

	mg/tab		mg/tab	
Crystalline Sodium Amoxycilli 91%*	961.	73.	961.	73.
Dried Microcrystalline Cellulos NF	305.	23.	273.	21.
Magnesium Stearate NF	1:	1.	1:	1.
xanthan gum 200 mesh**	1!	1.	5:	4.
Total	13	1Total	13	1

875 mg Amoxycillin Trihydrate Tablets with Xanthan Gum, 200 mesh

	mg/tab		mg/tab	
Amoxycillin Trihydrate 86%*	101'	78.	101'	78.
Dried Microcrystalline Cellulos NF	25(	19.	21'	16.
Magnesium Stearate NF	1:	1.	1:	1.
Xanthan Gum, 200 mesh**	1!	1.	5:	4.
Total	13	1Total	13	1

* adjusted for the potency of the amoxycillin component and corresponding to 875 mg amoxycillin,

** Xantural 75

Slow release layers may be formed using half the quantities given above, for a slow release layer comprising about 438 mg amoxycillin.

Immediate release layer - 1

Amoxycillin trihydrate	507 mg
(equiv. to amoxycillin free acid)	(438)
Potassium clavulanate	71.8

(equivalent to clavulanic acid)	(62.5)
Microcrystalline cellulose (Avicel PH102)	125
Sodium starch glycollate (Explotab)	26
Magnesium stearate	6.5

The immediate release layer comprises nominally 438/62.5 mg amoxycillin/clavulanate.

Immediate release layer - 2

Amoxycillin trihydrate	507mg
(equiv. to amoxycillin free acid)	(438)
Potassium clavulanate	71.8
(equivalent to clavulanic acid)	(62.5)
Microcrystalline cellulose (Avicel PH102)	135
Sodium starch glycollate (Explotab)	34
Talc	67
Magnesium stearate	25
Silica (Syloid)	17

The immediate release layer comprises nominally 438/62.5 mg amoxycillin/clavulanate.

Barrier Layers

Barrier layers and methods for their preparation are described in WO 95/20946 (SmithKline Beecham).

Preparation of Tablets

The active ingredients, fillers and diluents (microcrystalline cellulose), release controlling agents or disintegrants (crospovidone, sodium starch glycolate) and binders are mixed . Lubricants (talc, Mg-stearate) and colloidal silicon dioxide (Syloid 244) are added, and mixing is continued for another minute. The complete mixture is slugged on a tablet press or roller compacted (briquetting step), followed by size reduction (Apex, Fitzmill, Frewitt) and passage through an oscillatory sieve or particle size classifier (Kason, Sweco). If the flow properties are unsatisfactory, the briquetting step is repeated.

In some cases, where the bulk density is rather low, a densifying step (pre-tabletting and sieving as in the briquetting method) may be required in order to achieve the nominal weight of a particular layer.

Tablets may be coated with a white opaque coating, for instance the product Opadry, Opaspray (Colorcon).

Dissolution Testing Methods

The release of amoxycillin and clavulanate from tablets into static media may be measured using the U.S.P. Dissolution Test Method II.

Test specifications:

Temperature:	37.0 ± 0.5°C
Test medium:	Deionized waster

Method:

The drug release periodically up to 8 h is determined.

***In vivo* pharmacokinetic evaluation of formulations**

Formulations according to the present invention were evaluated in a human volunteer study.

Each formulation was administered with food and blood samples were taken 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h after dosing.

A combination of one tablet comprising 875/125 mg amoxycillin/clavulanate (Augmentin, SmithKline Beecham) and one tablet comprising 875 mg amoxycillin (Amoxyl, SmithKline Beecham) was used as a reference standard.

Results

The reference standard gave a median T_{max} of 1.50h, a mean C_{max} of 20.21µg/ml and a mean T_{MIC} of 4.24h (n=40), where T_{MIC} is the time above an amoxycillin concentration of 4µg/ml

In comparison, the existing Augmentin 875/125 mg tablet has a C_{max} value of 11.6±2.8 µg/ml (Physicians Desk Reference, Medical Economics Co, 52 edition, 1998, 2802). The time above MIC was about 40% of the 12 hour dosing interval for an MIC of 2 µg/ml and about 30% for an MIC of 4 µg/ml (SmithKline Beecham data).

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their

entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also incorporated by reference herein in its entirety in the manner described above for publications and references.

What is Claimed Is:

1. A tablet formulation comprising amoxycillin and potassium clavulanate in which all of the potassium clavulanate and part of the amoxycillin is in a first phase from which it is immediately released and the remainder of the amoxycillin in a second phase from which the amoxycillin is slowly released.

2. A tablet formulation comprising potassium clavulanate and a first part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for immediate release of the potassium clavulanate and amoxycillin and further comprising a second part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for slow release of amoxycillin.

3. A tablet formulation according to claim 1 in which the pharmacokinetic profile of the tablets will provide an amoxycillin C_{max} value in human plasma of at least 12 µg/ml.

4. A tablet formulation according to claim 1 in which the pharmacokinetic profile of the tablets will provide a mean plasma concentration of amoxycillin of at least 4 µg/ml for at least 4.4h.

5. A tablet formulation according to claim 1 in which amoxycillin and potassium clavulanate are present in a ratio by weight of from 1:1 to 30:1,

6. A tablet formulation according to claim 5 in which amoxycillin and potassium clavulanate are present in a ratio by weight of 10:1 to 20:1.

7. A tablet formulation according to claim 5 in which amoxycillin and potassium clavulanate are present in a ratio by weight of 11:1 to 17:1.

8. A tablet formulation according to claim 5 in which amoxycillin and potassium clavulanate are present in a ratio by weight of about 12:1, 14:1 or 16:1.

9. A tablet formulation according to claim 1 in which the portion of amoxycillin which is released immediately is provided as amoxycillin trihydrate or (crystalline) sodium amoxycillin or a mixture thereof whilst the portion of amoxycillin which is released

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slowly is provided as amoxycillin trihydrate or (crystalline) sodium amoxycillin or a mixture thereof.

10. A tablet formulation according to claim 9 in which amoxycillin is present in the immediate and slow release phases in a ratio of from 3:1 to 1:3.

11. A tablet formulation according to claim 10 in which amoxycillin is present in the immediate and slow release phases in a ratio of from 3:2 to 2:3.

12. A tablet formulation according to claim 10 in which amoxycillin is present in the immediate and slow release phases in a ratio of 3:2 to 1:1.

13. A tablet formulation according to claim 1 which comprises amoxycillin and potassium clavulanate in a 14:1 ratio, and comprises about 438 mg amoxycillin and about 62.5 mg of potassium clavulanate in the immediate release phase and about 438 mg of amoxycillin in the slow release phase.

14. A tablet formulation according to claim 1 which comprises amoxycillin and potassium clavulanate in a 16:1 ratio, and comprises about 563 mg amoxycillin and about 62.5 mg of potassium clavulanate in the immediate release phase and about 438 mg of amoxycillin in the slow release phase.

15. A tablet formulation according to claim 1 in which the immediate and slow release phases are provided as separate layers of a layered tablet.

16. A tablet formulation according to claim 15 in which the slow release layer comprises amoxycillin together with a release retarding excipient which allows for slow release of amoxycillin.

17. A tablet formulation according to claim 16 in which the release retarding excipient is selected from a pH sensitive polymers; a release-retarding polymer which has a high degree of swelling in contact with water or aqueous media; a polymeric material which form a gel on contact with water or aqueous media; and a polymeric material which have both swelling and gelling characteristics in contact with water or aqueous media.

18. A tablet formulation according to claim 17 in which the release retarding gellable polymer is selected from methylcellulose, carboxymethylcellulose, low-molecular

weight hydroxypropylmethylcellulose, low-molecular weight polyvinylalcohols, polyoxyethyleneglycols, and non-cross linked polyvinylpyrrolidone, or xanthan gum.

19. A tablet formulation according to claim 17 in which the release retarding gellable polymer is xanthan gum.

20. A tablet formulation according to claim 19 in which the xanthan gum is a fine mesh grade of xanthan gum.

21. A tablet formulation according to claim 20 in which the xanthan gum is pharmaceutical grade xanthan gum, 200 mesh.

22. A tablet formulation according to claim 19 in which the xanthan gum is present in from 0.5 to 25% by weight of the layer.

23. A tablet formulation according to claim 15 in which the slow release layer comprises from 70 to 80% of amoxycillin, from 0.5 to 25% of xanthan gum, from 10 to 30% of fillers/compression aids, and conventional quantities of lubricants.

24. A tablet formulation according to claim 23 in which the slow release layer comprises from 70 to 80% of amoxycillin, from 1.0 to 15%, of xanthan gum, from 15 to 30% of microcrystalline cellulose, and from 0.5 to 1.5% of magnesium stearate.

25. A kit comprising an immediate release tablet comprising amoxycillin and potassium clavulanate, optionally with a conventional (immediate release) tablet comprising amoxycillin, and a slow release tablet comprising amoxycillin (and no potassium clavulanate).

26.' A pharmaceutical tablet comprising amoxycillin (as the sole active ingredient) formulated with a release retarding excipient which causes a slow release of the amoxycillin from the tablet, and excluding tablets which comprise from 400 to 500 mg amoxycillin trihydrate or a mixture comprising at least 70% amoxycillin trihydrate and up to 30% sodium amoxycillin and hydroxypropyl methylcellulose.

27. A tablet according to claim 26 which comprises 100 to 1250 mg amoxycillin.

28. A tablet according to claim 26 in which the release retarding excipient is xanthan gum.

29. A tablet formulation according to claim 26 in which the xanthan gum is pharmaceutical grade xanthan gum, 200 mesh.

30. A tablet formulation according to claim 26 in which the xanthan gum is present in from 0.5 to 25% by weight of the layer.

31. A method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxycillin and potassium clavulanate in a tablet formulation comprising a first phase in which all of the potassium clavulanate and part of the amoxycillin is immediately released and a second phase comprising the remainder of the amoxycillin from which the amoxycillin is slowly released

32. A method according to claim 31 in which the infection is caused by the organisms *S pneumoniae* (including Drug Resistant *S pneumoniae*), *H influenzae* and/or *M catarrhalis*.

33. A method according to claim 31 in which the tablet formulation is taken at dosage intervals of 12h.

34. A pharmaceutical formulation comprising 1000 mg ±5% amoxycillin and 62.5 mg ±5% potassium clavulanic acid, in a nominal ratio of about 16:1, in combination with pharmaceutically acceptable excipients or carriers.

ABSTRACT

The present invention is directed to a tablet formulation comprising amoxycillin and potassium clavulanate in which all of the potassium clavulanate and part of the amoxycillin is in a first phase from which it is immediately released and the remainder of the amoxycillin in a second phase from which the amoxycillin is slowly released.

In a preferred embodiment the tablet formulation comprises potassium clavulanate and a first part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for immediate release of the potassium clavulanate and amoxycillin and further comprise a second part of amoxycillin formulated with pharmaceutically acceptable excipients which allow for slow release of amoxycillin.

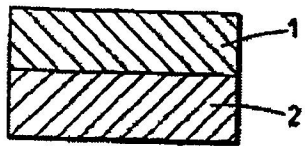


Fig. 1A

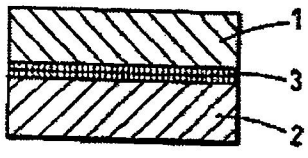


Fig. 1B

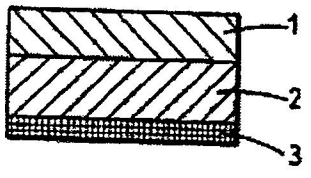


Fig. 1C

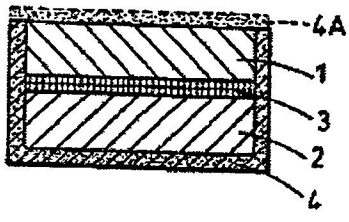


Fig. 1D

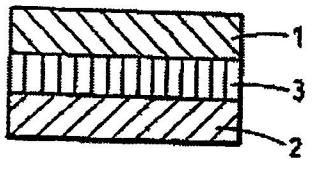


Fig. 1E